

ARTICLE

GENDER MATTERS: IMPLICATIONS FOR CLINICAL RESEARCH AND WOMEN'S HEALTH CARE

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I. INTRODUCTION

In recent years, heightened awareness of longstanding *biases* against women—in educational, economic, employment, and, most important, health-related opportunities—has catalyzed an expanded focus on women's issues. Past inattention to women's health issues in both the conduct of research and

clinical practice resulted in serious gaps in knowledge about the causes, treatment, and prevention of diseases in women.¹

It was over a decade ago that the United States Public Health Service Task Force on Women's Health Issues concluded that the exclusion of women in clinical research had significantly affected the quality of health care available to women.² Knowledge concerning the effects of various treatments on women and their unique needs remains sparse and underdeveloped.³ In addition, the majority of drugs have never been tested on pregnant women, primarily because of fetal protection policies that prohibit the inclusion of women of childbearing potential in most drug trials.⁴ This knowledge gap has left women unable to make informed reproductive and health care decisions. Thus, it has become clear that gender matters and that health care is no exception.⁵

1. OFFICE ON WOMEN'S HEALTH, U.S. PUBLIC HEALTH SERVICE, FACT SHEET: WOMEN'S HEALTH ISSUES (1995) (emphasis added). Women's health often is defined as including the normal biological processes, as well as all diseases, disorders, or conditions that affect women across the life span and that are unique to, more prevalent among, or more serious in women, or for which there are different risk factors or interventions for women than for men. See generally OFFICE OF RESEARCH ON WOMEN'S HEALTH, NATIONAL INSTITUTES OF HEALTH, REPORT OF THE NATIONAL INSTITUTES OF HEALTH: OPPORTUNITY FOR RESEARCH ON WOMEN'S HEALTH (1991) [hereinafter ORWH REPORT]; Task Force on Women's Health Issues, U.S. Public Health Service, *Women's Health: Report of the Public Health Service Task Force on Women's Health Issues*, 100 PUB. HEALTH REP. 73 (1985) [hereinafter Task Force Report]. It is important to recognize that "women" are a large, heterogeneous group—women of color, women with disabilities, girls, adolescents, postmenopausal women, homeless women, immigrant women. To incorporate the distinctive and sometimes disparate needs of all women requires tackling the psychosocial issues that contextualize specific medical problems: racism, sexism, violence against women, gender roles, poverty, and health beliefs. See Task Force Report, *supra*, at 85 (noting that research and service programs addressing women's health must address "enduring characteristics [such] as age, race, or ethnicity as well as . . . marital and household status, urban or rural living, education, occupation, and income").

2. See Task Force Report, *supra* note 1, at 82 ("A systematic effort must be made to address issues relating to *gender bias*, in research and clinical practice, that lead to inadequate attention to the needs of women." (emphasis added)).

3. See 1 COMMITTEE ON THE ETHICAL AND LEGAL ISSUES, INSTITUTE OF MEDICINE, WOMEN AND HEALTH RESEARCH: ETHICAL AND LEGAL ISSUES OF INCLUDING WOMEN IN CLINICAL STUDIES 27 (Anna C. Mastroianni et al. eds, 1994) [hereinafter WOMEN AND HEALTH RESEARCH]. The two main concerns include the lack of knowledge concerning gender differences in relation to health problems common to both men and women and lack of investigations of health problems specific to women. See *id.*

4. See L. Elizabeth Bowles, *The Disenfranchisement of Fertile Women in Clinical Trials: The Legal Ramifications of and Solutions for Rectifying the Knowledge Gap*, 45 VAND L. REV. 877, 883 (1992).

5. See generally Karen H. Rothenberg, *New Perspectives for Teaching and Scholarship: The Role of Gender in Law and Health Care*, 54 MD. L. REV. 473, 480 (1995) ("[G]ender does matter in the context of both law and biomedical sciences.").

Over the last few years, data gathered by women's health advocates have caught the attention of researchers, policymakers, and the general public.⁶ As a result, legislative and regulatory changes have begun to promote the inclusion of women in clinical research.⁷ It is hoped that a better understanding of women's health issues and gender differences will lead to the removal of barriers to quality health care for American women.

This Article examines gender bias in health care and the legal and ethical ramifications of including women in research and in improving their access to health care.⁸ Part II reviews the pervasiveness of gender bias in health care. It highlights numerous examples of how gender bias creates barriers to all levels of women's health, from clinical research to the delivery of health care services, and explores the reasons for these barriers, including societal attitudes and gender differences in communication. Part III reviews the historical development of regulatory policies designed to protect human subjects from research risks. It argues that federal regulations restricting the participation of women in clinical trials codified societal distrust of women's capacity to decide what was best for them, their fetuses, and families. The evolution toward inclusion is discussed in this historical context as the focus shifts from protecting "vulnerable" women (or their fetuses) from the burdens of experimentation to increasing the inclusion of women in clinical trials in order to benefit their health. While new regulations purport to increase inclusion of women, they do not answer the most difficult questions involving pregnant women.

Part IV explores the ethical and legal ramifications of gender bias, primarily in the context of clinical research, as a non-financial barrier to health care. More specifically, it explores the policy underpinnings of the Supreme Court's recognition in

6. See ORWH REPORT, *supra* note 1, at 7 (describing the lack of knowledge about women's health as "a crisis that has stunned citizens, policymakers, and the biomedical community"). The report concluded that women will become the larger population and will find themselves most susceptible to disease in the future. See *id.* It also pointed out that some conditions are uniquely female or affect women differently than men. See *id.*

7. Refer to Parts II and III *infra*.

8. This Article is limited to an analysis of gender "bias" as a nonfinancial barrier to health care. Obviously, financial barriers significantly impede women's access to health care. For example, women are disproportionately employed in temporary or low-paying service jobs that do not provide health benefits. Of the 35 million uninsured Americans, almost 12 million are adult women between the ages of 18 and 65. See THE AMERICAN WOMAN: 1994-95, WHERE WE STAND, WOMEN AND HEALTH, 27, 144 (Cynthia Costello & Anne J. Stone eds., 1994) [hereinafter THE AMERICAN WOMAN]. There are many more million women that are underinsured, particularly with respect to access to needed preventive services. See *id.*

*UAW v. Johnson Controls, Inc.*⁹ that women can be trusted to make appropriate decisions concerning their reproductive health and that differential application of privileges to men and women constitutes gender discrimination.

Part IV then analyzes the constitutional issues, particularly with respect to the liberty and privacy interests of women, raised by the regulatory barriers to the participation of women in clinical research and current paternal consent requirements. It also considers the equal protection issues raised by underinclusion and overinclusion of women relative to men in clinical research.

Part IV continues with an analysis of federal and state antidiscrimination statutes and their application to both clinical research and health care access. Finally, it concludes with a discussion of the tort liability issues raised by the participation of women in clinical research. Historically, drug manufacturers and researchers excluded women from their clinical trials, in part, for fear of liability resulting from harm to potential offspring. In the future, however, liability will likely be based on the exclusion of women as the standard of care develops to adapt drugs and treatment to gender differences based on clinical research.

Finally, Part V concludes with a discussion of major policy considerations that are largely based on the work of the Institute of Medicine's Committee on the Ethical and Legal Issues Relating to the Inclusion of Women in Clinical Studies. It also highlights the need to reform our national research agenda, health professional education, and the representation of women in science and medicine. Even more basically, it concludes that we must recognize that gender matters in the way we view women and their decisionmaking capabilities, in the way patients and providers communicate, and ultimately, in the way health care is delivered.

II. GENDER BIAS: REALITIES AND REASONS

[T]he vast majority of women's health concerns . . . are the same as men's but all too often aren't taken as seriously, treated as appropriately, or understood as well.¹⁰

9. 499 U.S. 187 (1991). *Johnson Controls* involved a Title VII challenge to a fetal protection policy in the workplace. See *id.* at 192. For further discussion of its application to gender bias in clinical research and health care, refer to subpart IV(A) *infra*.

10. LESLIE LAURENCE & BETH WEINHOUSE, OUTRAGEOUS PRACTICES: THE ALARMING TRUTH ABOUT HOW MEDICINE MISTREATS WOMEN 7 (1994).

Medicine is only as good as the knowledge it's based on, and the best doctor in the world can't compensate for faulty research.¹¹

For the most part, the lack of knowledge about women's health has resulted from our failure to research women's health issues. Commentators point to the reinforcement of gender attitudes and the history of protectionism that have led to current gaps in medical knowledge.¹² Several notions associated with gender have contributed to the systematic exclusion of women from clinical research. These factors include the perception of men as the "norm," the idea that hormonal differences in women will "complicate" research results and increase costs, the traditional role of women, and the primarily male-dominated research community.¹³ For pregnant women, these barriers are also entangled with potential risks to the fetus and the associated liability that might follow.¹⁴

Science has a long history of viewing men as the standard by which all things are measured. "Like the pronoun 'he,' it was taken for granted that the white male subject stood for all of us."¹⁵ Because the research community views men as the norm, they see differences in women as unknown variables that tend to confound results. For example, women present factors such as menstrual cycles, pregnancy, teratogenic liability, and menopause.¹⁶ Some researchers argue that these factors complicate research and add excess costs to experimentation.¹⁷ Paradoxically, "scientists seem to be confirming that women's bodies are different and more difficult to study. But then by simply extending their male-drawn conclusions to women, they are implying that—with a few obvious exceptions—women's bodies are the same as men's."¹⁸ These assumptions have discouraged studies on females and have fostered ignorance concerning the special needs of women.¹⁹

11. *Id.* at 3.

12. *See, e.g.,* Rebecca Dresser, *Wanted: Single, White Male for Medical Research*, 22 HASTINGS CENTER REP. 24, 24 (1992).

13. *See id.* at 25-26, 27-28.

14. *See id.* at 25.

15. *Id.* at 27.

16. *See* Bowles, *supra* note 4, at 881.

17. *See* Tracy Johnson & Elizabeth Fee, *Women's Participation in Clinical Research: From Protectionism to Access*, in 2 WOMEN AND HEALTH RESEARCH, *supra* note 3, at 6.

18. LAURENCE & WEINHOUSE, *supra* note 10, at 4.

19. *See id.* (noting that instead of seeking solutions to some of the problems presented with studying women, "scientists have simply taken the easy way out and studied men").

The perception of the middle-aged white male as the normal economic distributor and an emphasis on the economic costs of health care also may have led to this disproportionate concern for the health of men.²⁰ In addition to outnumbering women in positions of political influence, men also dominate in the medical research community.²¹ Although the proportion of women in medical schools has risen steadily in the last decade to approximately forty percent,²² women still constitute a minority of medical researchers and a small percentage of those making funding decisions.²³ Naturally, policymakers and researchers prioritize issues according to their most personal interests.²⁴ As a result, women's concerns, as well as the underlying variables of race, ethnicity, socioeconomic status, and sexual orientation, have not been given the attention they deserve.²⁵ Because men dominate the decisionmaking community, the social worth judgments of how to allocate funds also favor research on men.²⁶

The Public Health Task Force on Women's Health Issues concluded that many methodological problems, as well as lack of data, limit the ability to understand the status of women's health and women's particular health care needs.²⁷ In study after study of health issues important to women, women have been excluded or seriously underrepresented.

20. See Dresser, *supra* note 12, at 28 (maintaining that an emphasis on the economic costs of disease may lead to disproportionate amounts of research on the young or middle-aged white male).

21. See *id.* (noting that science "has been and to some extent still is largely populated by white males").

22. See ASSOCIATION OF AMERICAN MEDICAL COLLEGES, WOMEN IN U.S. ACADEMIC MEDICINE: STATISTICS 1995, at 1 (1995) (citing a 41% figure).

23. See Bowles, *supra* note 4, at 883.

24. See LAURENCE & WEINHOUSE, *supra* note 10, at 5 (relating a female NIH doctor's observation that "[y]ou want doctors to study what they're interested in, so you have male doctors in their fifties studying other male doctors in their fifties for heart attacks").

25. See 1 WOMEN AND HEALTH RESEARCH, *supra* note 3, at 114 (indicating that a growing body of evidence indicates that these variables have a significant impact on health and should be examined in clinical studies).

26. Members of the dominant group see themselves as "objective" and the existing social structure as "natural." Dresser, *supra* note 12, at 27-28. Accordingly, the "special money" necessary for studies of women and minorities reflects the social worth judgment that "regular money" should be reserved for "normal" research on the group with greater socially determined priority, white males. *Id.* at 28.

27. See Task Force Report, *supra* note 1, at 81.

A. Gender Gaps in Clinical Research

Perhaps the most shocking example of the exclusion of women from the clinical study of a health condition that almost exclusively affects women was a project that examined the impact of obesity on breast and uterine cancer. The study participants were all men.²⁸ For twenty years, women were also excluded from the Baltimore Longitudinal Study of Aging, one of the largest studies of the natural process of aging.²⁹ Six years after women were permitted to participate, a report of the study findings entitled "Normal Human Aging" was published.³⁰ It is considered the definitive study of aging in the United States. It contains no data on women.³¹

Women were also frequently left out of clinical trials of experimental AIDS therapies,³² yet women now represent the fastest growing population with AIDS.³³ Of the 28 trials of drugs designed to fight HIV, only 131 of 2634 participants were women.³⁴ In addition, when the FDA approved AZT in 1987, not one of the 63 federally-sponsored studies had analyzed its effects on women.³⁵

The effects of exclusion from clinical research are far reaching. All women suffer the consequences of studies that include only men, or that include women, but do not adequately analyze any gender-related differences. Because of the research gap, "physicians now frequently lack adequate evidence on whether women . . . will be helped, harmed, or not affected at all by numerous therapies now endorsed as promoting 'human

28. See *id.* at 24. The author further noted that the study examined the effects of particular nutrients on estrogen metabolism, and researchers chose only male subjects in the belief that estrogen metabolism is similar in men and women. See *id.* at 29 n.2.

29. See LAURENCE & WEINHOUSE, *supra* note 10, at 61. Women are the "aging majority" in this country. As of 1990, women represent almost 60% of the population over 65 and 72% of the population over 85. ORWH REPORT, *supra* note 1, at 9. Women also have an average life expectancy of 78.6 years, almost 7 years longer than men. *Id.* at 8.

30. See LAURENCE & WEINHOUSE, *supra* note 10, at 61.

31. See *id.*

32. See *id.* at 144 (quoting one doctor's observation that "[w]e don't know a lot about HIV in women because almost all the studies that were done originally were done on men").

33. ORWH REPORT, *supra* note 1, at 10.

34. LAURENCE & WEINHOUSE, *supra* note 10, at 149. For example, women represented only 5.3% of the research subjects in studies testing drugs for cytomegalovirus retinitis, 7.1% for mycobacterium avium complex, and 7.9% for pneumocystis carinii pneumonia therapy—yet women with AIDS succumb to these infections at the same rate as men with AIDS. *Id.* at 149-50.

35. *Id.* at 5.

health.³⁶ It is not surprising that women experienced toxic side effects when given AZT dosages to treat AIDS calibrated to the ever-popular seventy-kilogram male.³⁷ Physicians treating women with AIDS are still left guessing at drug dosing.³⁸ When the results of the study comparing the benefits of AZT to the drug deoxyinosine were released in 1992, only four percent of the participants were female, too small a percentage to provide meaningful information to physicians about drug treatment regimens.³⁹

Several well-known studies of cardiovascular disease considered only male subjects.⁴⁰ Although they have had a significant impact on the treatment and prevention of heart disease in men, these studies have not produced definitive information about prevention and treatment of women's heart disease.⁴¹ In fact, the lack of research on women's health and gender-blind health conditions in women may have a dangerous effect.⁴² Based on the findings of studies of heart disease and cholesterol that included men only, the American Heart Association recommended a diet that could actually elevate the risk of heart disease for women.⁴³ A study of 51,529 male health professionals begun in 1986 suggested that moderate drinking and a decrease in heart disease are causally related.⁴⁴ It is unclear, however, whether the result of this study can be extrapolated for application to women's health. For example, unlike men,

36. Dresser, *supra* note 12, at 24.

37. See LAURENCE & WEINHOUSE, *supra* note 10, at 5.

38. See *id.* at 150.

39. See *id.*

40. See EDWARD B. DIETRICH & CAROL COHAN, WOMEN AND HEART DISEASE 11-12 (1992); 1 WOMEN AND HEALTH RESEARCH, *supra* note 3, at 65.

41. See 1 WOMEN AND HEALTH RESEARCH, *supra* note 3, at 65; see also Nanette K. Wenger, *Exclusion of the Elderly and Women from Coronary Trials: Is Their Quality of Care Compromised?*, 268 JAMA 1460, 1460-61 (1992) (reporting that exclusion of women from studies because of an assumption that cardiovascular disease is comparable in women and men "has resulted in sizable gaps in our knowledge about gender differences in efficacy of preventive strategies, . . . diagnostic methods, responses to medical and surgical therapies, and clinical outcomes for coronary heart disease"). One physician has said, "If a fifty-year-old man goes to the doctor complaining of chest pains, the next day he will be on a treadmill taking a stress test. If a fifty-year old woman goes to the doctor and complains of chest pains, she will be told to go home and rest." Dresser, *supra* note 12, at 26.

42. In the Hypertension Detection and Follow-Up study, 168% more women who were given "stepped care" treatment died than women who were on control. See Vanessa Merton, *The Exclusion of Pregnant, Pregnable and Once-Pregnable People (a.k.a. Women) from Biomedical Research*, 19 AM. J.L. & MED. 369, 383 & n.57 (1993).

43. See Dresser, *supra* note 12, at 27.

44. See Eric B. Rimm et al., *Prospective Study of Alcohol Consumption and Risk of Coronary Disease in Men*, 338 LANCET 464, 464 (1991).

"women who consume moderate quantities of alcohol have an increased risk of breast cancer."⁴⁵

In 1988, the results of a government funded study of 20,000 male physicians revealed that small doses of aspirin would help prevent heart attacks.⁴⁶

Physicians were thought to be the ideal subjects, knowledgeable and disciplined, and able to comply with complicated research protocols. Women, who comprised 10 percent of physicians in the United States at the time, were excluded from the study. Nurses, the vast majority of whom were women, apparently weren't considered up to the task.⁴⁷

B. *Gender Disparities in Clinical Decisionmaking*

Gender bias extends beyond clinical research into all areas of health care: "[I]t pervades medicine, beginning with medical-school admissions and education, encompassing research facilities and medical journals, and culminating in how women are treated as patients in clinics, hospitals, and physicians' offices across the country."⁴⁸ For example, men are more likely to be referred for diagnostic testing for lung cancer than women, even where risk factors are equal between the two genders.⁴⁹ Women in need of kidney dialysis are approximately 30% less likely to receive a transplant than men.⁵⁰ Men are 6.5 times more likely to be referred for cardiac catheterization than women.⁵¹ At the same time, 26% of men versus 14% of women receive clot-dissolving drugs after a heart attack.⁵² Further, another study indicated that physicians are twice as likely to attribute symptoms of heart disease in women to psychiatric and

45. Charles Fuchs et al., *Alcohol Consumption and Mortality Among Women*, 332 NEW ENG. J. MED. 1245, 1245 (1995). The study also found that, while light to moderate drinking is associated with decreased cardiovascular deaths in women, this benefit applies mainly to older women and those women otherwise at risk for coronary disease. See *id.* at 1249.

46. See THE AMERICAN WOMAN, *supra* note 8, at 91. Unfortunately, there was no data to substantiate whether an aspirin a day for women would have any impact on their risk of heart disease.

47. *Id.*

48. LAURENCE & WEINHOUSE, *supra* note 10, at 5.

49. See Council on Ethical & Judicial Affairs, American Medical Ass'n, *Gender Disparities in Clinical Decision Making*, 266 JAMA 559, 560 (1991) [hereinafter *Gender Disparities*] (reporting that among men and women with similar smoking habits, men were twice as likely to receive cytologic studies of sputum; even after smoking status and other medical considerations were taken into account, men still had 1.6 times the chance of receiving cytologic testing).

50. *Id.*

51. *Id.*

52. See LAURENCE & WEINHOUSE, *supra* note 10, at 104.

noncardiac causes.⁵³

With respect to AIDS, it was not until 1993 that the Center for Disease Control (CDC) amended its presumptive definition of AIDS to include those manifestations most common in women, *i.e.*, cervical cancer, pelvic inflammatory disease, and vaginal yeast infections.⁵⁴ After the change, thousands more women were classified as having AIDS.⁵⁵ Even after being diagnosed and entering treatment, women still receive fewer services than men. For example, a male injection drug user (IDU) with AIDS is 20% more likely to be hospitalized than a woman with AIDS, and then the hospital costs of treating a male IDU with AIDS is over \$9000 more per year than the hospital care costs of treating a woman with AIDS.⁵⁶ It is also worth noting that a large prospective study conducted by Terry Beirn Community Programs for Clinical Research on AIDS recently found that HIV-infected women face an increased risk of death when compared with men.⁵⁷ The authors of the study suggest that the reasons for excess mortality in HIV-infected women might include lower socioeconomic status, domestic violence, and the lack of social support,⁵⁸ factors that reflect differential access to health care for women.⁵⁹

C. *The Role of Gender in the Physician-Patient Relationship*

Bias has also been reported in studies that evaluate the relationship between the gender of a physician and the offering of gender-sensitive diagnostic practices, such as breast exams, pap smears, and mammograms. Women who reported having a male physician as their usual provider were less likely to receive pap tests and mammograms than women who reported having a female physician as their usual care provider.⁶⁰ There

53. See *Gender Disparities*, *supra* note 49, at 560.

54. See LAURENCE & WEINHOUSE, *supra* note 10, at 148-49.

55. See *id.*

56. See Fred J. Hellinger, *The Use of Health Services by Women with HIV Infection*, 28 HEALTH SERVICES RES. 543, 543 (1993).

57. See Sandra L. Melnick et al., *Survival and Disease Progression According to Gender of Patients with HIV Infection: The Terry Beirn Community Programs for Clinical Research on AIDS*, 272 JAMA 1915, 1915 (1994).

58. See *id.* at 1919. During a 15 month period of observation, women had significantly lower rate of survival than men, even though disease progression rates did not differ significantly by gender. *Id.*

59. See *id.* at 1915.

60. See Peter Franks & Carolyn M. Clancy, *Physician Gender Bias in Clinical Decisionmaking: Screening for Cancer in Primary Care*, 31 MED. CARE 213, 213 (1993).

was a similar but insignificant trend for breast exams.⁶¹ These results persisted after "multivariate adjustment for patient age, race, education, income, insurance status, subjective health status, other health behaviors, and attitudes toward health care and health insurance."⁶²

In another study, rates of pap smears and mammograms ordered were consistently higher for female physicians than for male physicians.⁶³ The difference was particularly significant between physicians in internal medicine and family practice.⁶⁴ Women physicians may be more likely to exercise greater diligence in initially and repeatedly offering screening tests.⁶⁵ They also may communicate the risk of cancer more effectively.⁶⁶ Women patients may be more likely to follow through in obtaining tests suggested by women physicians because they are more comfortable discussing issues of concern with female physicians.⁶⁷

In her book, *You Just Don't Understand*, Deborah Tannen has described differences in the communication styles of men and women.⁶⁸ Some of these differences may, in part, explain why gender matters in medical care. Because communication is the fundamental instrument by which physician and patient relate to each other and attempt to achieve therapeutic goals, the relationship between physician and patient is central to the process of health care delivery. Physicians must promote trust—they must hear the patient's story.

As one author has observed, "institutional authority of the physician and acquiescence to that authority by the patient, fostered frequently by gender expectations, can make it difficult for patients to assert their informational needs."⁶⁹ For example, women who believe they have serious diseases may present their worries in a vague manner in an effort to avoid being labeled hypochondriacs.⁷⁰

61. *Id.* at 216-17.

62. *Id.* at 213.

63. See Nicole Lurie et al., *Preventive Care for Women: Does the Sex of the Physician Matter?*, 329 NEW ENG. J. MED. 478, 479 (1993).

64. See *id.* at 481.

65. See *id.*

66. See *id.*

67. See *id.*

68. See DEBORAH TANNEN, *YOU JUST DON'T UNDERSTAND* (1990).

69. M. Robin DiMatteo, *The Physician-Patient Relationship: Effects on the Quality of Health Care*, 37 CLINICAL OBSTETRICS & GYNECOLOGY 149, 153 (1994).

70. See Kirsti Malterud, *Strategies for Empowering Women's Voices in the Medical Culture*, 14 HEALTH CARE FOR WOMEN INT'L 365, 370 (1993); see also Leifur Dungal, *Physicians' Responses to Patients: A Study of Factors Involved in the Office Interview*, 6 J. FAM. PRAC. 1065, 1069 (1978) (finding that physicians express anxi-

The most difficult physician-patient relationships tend to be between male physicians and female patients. Some research has shown that male physicians may discourage information exchange with female patients. For example, compared to male physicians, female physicians engage in significantly more positive talk, partnership-building, question-asking, and information-giving.⁷¹ Similarly, when with female physicians, patients talk more during the medical visit and appear to participate more actively in the medical dialogue.⁷² The longest visits are between female physicians and female patients and the shortest between male physicians and female patients.⁷³

Both male and female patients are more willing to disclose symptoms to a physician of the same sex than to a physician of opposite sex. Research has shown that female-female interactions are characterized by fewer interruptions of patients by physicians.⁷⁴ Fear and embarrassment may in fact be further barriers to health care, especially among special population groups, including low income blacks, hispanics, and women over fifty.⁷⁵

A few recent studies have, in fact, surveyed women's attitudes about physician-patient communication. In the 1993 Commonwealth Fund study of over 2500 women and 1000 men, 1 out of 4 women (compared to 12% of men) said that they had been "talked down to" or treated like a child by their physician.⁷⁶ Nearly 1 out of 5 women (compared to 7% of men) had been told that a reported medical condition was "all in [your]

ety, frustration, and less comfort when treating female patients).

71. See Debra Roter et al., *Sex Differences in Patients' and Physicians' Communication During Primary Care Medical Visits*, 29 MED. CARE 1083, 1089 (1991).

72. See Nancy Zare et al., *Sex of Provider as a Variable in Effective Genetic Counseling*, 19 SOC. SCI. & MED. 671, 674 (1984) (noting that women who received genetic counseling from female physicians discussed a wider variety of topics and addressed more "care counseling issues" than women who were counseled by male physicians).

73. See Roter et al., *supra* note 71, at 1087 (indicating that visits with female doctors led to one-third more total statements than with male doctors). Communication seems to be enhanced with same sex dyads when (1) the patient prefers to be treated by a physician of the same sex, (2) sex-specific conditions are being addressed, (3) conditions of a highly personal or sensitive nature are being treated such that sex or sexuality are especially relevant, or (4) when a long-term relationship between physician and patient is required. See Carol S. Weisman, *Women and Their Health Care Providers: A Matter of Communication: Communications Between Women and Their Health Care Providers: Research Findings and Unanswered Questions*, 102 PUB. HEALTH REP. 147, 150 (Supp. 1987).

74. See Weisman, *supra* note 73, at 150.

75. See Kathy Coyne et al., *Reaching Special Populations with Breast and Cervical Cancer Public Education*, 7 J. CANCER EDUC. 293, 293 (1992).

76. COMMONWEALTH FUND, SURVEY OF WOMEN'S HEALTH 7 (1993).

head.'"⁷⁷

A recent Gallop survey of 833 women aged 45-60 found that the physical and emotional effects of menopause most frequently cited as the greatest concerns were osteoporosis, emotional well-being, and heart disease.⁷⁸ Of the women who reported these conditions, only about half said their physicians had discussed emotional symptoms or heart disease with them, while two-thirds said that their physicians had discussed osteoporosis.⁷⁹ Instead, physicians were more likely to discuss short-term physical symptoms such as hot flashes and night sweats.⁸⁰

Communication barriers may be of particular concern to the older female population.⁸¹ In addition to sensory losses and concerns about the use of medical jargon, psychosocial factors were a major concern.⁸² Older women may fear being labelled as a nuisance, hypochondriac, or "crabby old woman."⁸³ Many older women report being intimidated by doctors and consider them as god-like entities who are busy with important matters and should not be bothered with their trivial aches and pains.⁸⁴ Older women may feel particularly timid about private or embarrassing information and are likely to accept poorly communicated explanations, believing they are the ones who are at fault.⁸⁵

In another study, health care professionals' impressions of women with cancer were compared with their impressions of women with other serious diseases.⁸⁶ All the professionals thought they would feel more tense treating a woman who had been diagnosed with breast cancer or lung cancer or who had been burned severely than a woman who had experienced a

77. *Id.* In general, women reported greater communication problems with their physicians and were more likely to change doctors because of their dissatisfaction (41% of all women versus 27% of men). *Id.* Though women of color were less satisfied with their physicians than white women, they were less likely to change physicians or to have access to health care choices. *Id.* at 10.

78. See Teri Randall, *Women Need More and Better Information on Menopause from Their Physicians, Says Survey*, 270 JAMA 1664, 1664 (1993).

79. See *id.*

80. See *id.*

81. See M. Jean Root, *Women and Their Health Care Providers: A Matter of Communication: Communication Barriers Between Older Women and Physicians*, 102 PUB. HEALTH REP. 152, 152 (Supp. 1987).

82. See *id.* at 154.

83. *Id.* at 155.

84. See *id.*

85. See *id.*

86. See Kimeron N. Hardin & B. Jo Hailey, *Health Care Professionals' Perceptions of Seriously Ill Women*, 14 HEALTH CARE FOR WOMEN INT'L 7, 7 (1993).

heart attack.⁸⁷ The study also examined how different categories of health care professions perceive emotional issues surrounding serious illness.⁸⁸ It concluded that nurses and psychologists perceived more need for psychological counseling than did physicians.⁸⁹

In the context of contraception and reproductive health, the contrast becomes clear between the provider's biomedical assumptions based on physiological orientation and the woman's contextual understandings based on knowledge of their social lives.⁹⁰ Of even more importance is that medical dominance over the parameters of interaction produces inadequate communication, which in turn leads to inadequate medical care.⁹¹ Physicians may cut off women when they try to raise topics that are not directly medical in nature.⁹² Women come to physicians for help and understanding on how to adjust their bodies to their social lives, whereas the medical model assumes that women should adjust their social lives to their bodies.⁹³

Gender differences may be further compounded by the dependency and inequality inherent in the provider-patient relationship.⁹⁴ When the power between the parties is unequally distributed, effective participation is undermined and control

87. See *id.* at 14.

88. See *id.* at 10.

89. See *id.* Provider gender may have influenced these results because most of the nurses were women while most of the physicians were men. See *id.* Previous research had found that physicians overrated the importance of pain on cancer patients and underrated the importance that the patients placed on disruption of leisure activities. See *id.* at 8-9. That previous research also revealed that nurses overrated the importance of physical appearance changes and underrated being able to complete routine household chores. See *id.* at 9. In addition, other research had found that personal reactions of health care providers to diagnoses could affect their ability to provide objective and comprehensive care. See *id.*

90. See ALEXANDRA D. TODD, *INTIMATE ADVERSARIES: CULTURAL CONFLICT BETWEEN DOCTORS AND WOMEN PATIENTS* 5 (1989) ("Contraception, then, illuminates problems in the doctor-patient relationship in general and the doctor-female patient relationship in particular.").

91.

Thus doctors who are the group that most needs to hear what patients and critics are saying, are the least likely group to be listening. . . . The doctor-patient relationship, however, carries a special impetus to avoid such misunderstanding It can contribute to control or lack of control over reproductive processes, it can improve or decrease health; it can mean life or death.

Id. at 6.

92. See *id.* at 5 (noting that the "subtler question" of which topics are allowed is rarely addressed).

93. See *id.* at 4.

94. See Patricia Peppin, *Power and Disadvantage in Medical Relationships*, 3 TEX. J. WOMEN & L. 221, 222 (1994).

of the ultimate decision is minimized.⁹⁵ Without power, patients cannot give effect to their own values without difficulty, whether on a personal, cultural, religious, or otherwise group-defined basis.⁹⁶ When patients find themselves unable to control decisionmaking, the likelihood increases that unwanted risks may be imposed on them.⁹⁷

Ironically, all this medical attention may harm women, as evidenced by recent concerns about high rates of hysterectomies and cesarean sections.⁹⁸ In the area of mental health, women are consistently treated more frequently and more aggressively than men. For example, numerous studies conducted over the last twenty years have shown that when men and women present the same physical or emotional complaints, women are significantly more likely to receive antidepressants, tranquilizers, and other psychotropic drugs.⁹⁹

In fact, women do use health services more than men.¹⁰⁰ Nevertheless, the effects of gender on the doctor-patient relationship may undermine the value of the health care they receive. Even though women use more health services and report more symptoms,¹⁰¹ we still do not know whether women and men seeking health care differ in the number or types of symptoms they disclose to the physician.¹⁰² Women may ask more questions, but we do not know why.¹⁰³ It could be attributed to greater exposure to sources of health information, to greater acceptance of health-seeking roles, or to less clear information women receive from their physicians.¹⁰⁴

As noted earlier, women's roles and experiences within the health care system differ from those of men. Professional patterns of dominance not only mirror, but reinforce social expectations of men as knowledgeable authorities and of women as deferential servants who follow but do not initiate treatment programs. The gender imbalance within health care structures

95. See *id.* at 223.

96. See *id.*

97. See *id.*

98. See LAURENCE & WEINHOUSE, *supra* note 10, at 171, 180.

99. Women receive 73% of all prescriptions written for psychotropic medication (the figure rises to 90% when the prescribing physician is not a psychiatrist). *Id.* at 275-76. Women receive up to 83% of prescriptions for antidepressants, which exceeds the 66% that one would expect to be based on the two-to-one female-to-male ratio for depression. *Id.* at 276. It has been suggested that women's disadvantaged position in society puts them at a higher risk for mental illness. See *id.*

100. See Weisman, *supra* note 73, at 147.

101. See *id.*

102. See *id.* at 148.

103. See *id.*

104. See *id.*

encourages doctors to accept prevailing social attitudes about women and illness. In appropriating the authority to define what is normal and healthy for women, male professionals have ensured women's continuing dependency on them.

It is this traditional role of women that has, in fact, reinforced the exclusion of women from clinical research.¹⁰⁵ Until recent decades, men served as the providers and women as the caregivers.¹⁰⁶ Society has placed an emphasis on women as instruments of reproduction rather than on women as individuals with unique personal concerns and needs.¹⁰⁷ Thus, in considering the relative worth of women, the medical community tended to value reproductive issues over the general health of women.¹⁰⁸

All of these gender-based obstacles increase exponentially for pregnant women, who face the added consideration of balancing their own health needs with associated risks to the fetus. Society has created the expectation that a woman must always place the well-being of her child before all other concerns.¹⁰⁹ Thus, the pregnant woman bears the highest moral, ethical, and legal responsibilities to her fetus.¹¹⁰ Furthermore, society may stigmatize a woman who does not make an "acceptable" decision concerning her own health and its relation to that of the fetus:

A woman who refuses medical treatment is seen as irrational if she chooses to rely on the forces of nature or the will of God, rather than on the technological intervention of her physician; she is irrational if she trusts the medical establishment less than she trusts her own moral or medical judgment; she is irrational if she fears her own death more than she fears the death of the fetus. She demonstrates her rationality by a willingness to deny her self-interest and relinquish her moral decision-making power.¹¹¹

By establishing protectionist policies in clinical research and health care, society has wrestled the decisionmaking power

105. See Merton, *supra* note 42, at 386 n.78.

106. See *id.* at 386.

107. See *id.* (noting the biomedical research community's "obsession" with the possibility of pregnancy).

108. See *id.*

109. See CYNTHIA R. DANIELS, *AT WOMEN'S EXPENSE: STATE POWER AND THE POLITICS OF FETAL RIGHTS* 1 (1993) (arguing that the "notion that the fetus has rights, as a patient and a citizen, separate from the pregnant woman's, has generated a deep crisis in reproductive relations in the United States").

110. See *id.* at 2 (maintaining that the mother's rights "are potentially made contingent by fetal rights").

111. *Id.* at 48-49.

away from women and reinforced the pregnant woman's obligation to conform to social expectations concerning traditional gender roles. In essence, protectionism devalues women as individuals and characterizes them as vulnerable vessels of reproduction, incapable of making the correct choices concerning their health and that of their own offspring.¹¹² It is this premise, in fact, that puts into context the evolution of regulatory barriers that excluded women from clinical research.

III. THE EVOLUTION OF REGULATION: PROTECTIONISM, PITFALLS, AND PROGRESS

The participation of human subjects in biomedical and behavioral research is governed by two sets of federal regulations promulgated by the Department of Health, Education, and Welfare (DHEW) and its successor, the Department of Health and Human Services (DHHS). The first set of regulations is DHHS's Protection of Human Subjects Regulations,¹¹³ which apply to all biomedical and behavioral research conducted by DHHS or funded in whole or in part by a Department grant, contract, cooperative agreement, or fellowship.¹¹⁴ These regulations enumerate general protections for all human subjects plus additional safeguards for segments of the population who lack the capacity to give informed consent (*i.e.*, children)¹¹⁵ or are particularly vulnerable to coercion (*i.e.*, prisoners).¹¹⁶ Pregnant women are designated also as a class of "vulnerable" human subjects who are in need of special protection under these regulations.¹¹⁷

112. See Merton, *supra* note 42, at 386 (arguing that exclusionary criteria reinforce a cultural stereotype that is harmful to the interest and progress of women).

113. Protection of Human Subjects, 45 C.F.R. §§ 46.101-409 (1994). In June 1991, the Basic DHHS Policy for Protection of Human Research Subjects, often referred to as Subpart A, was replaced by the Federal Policy for the Protection of Human Subjects, 45 C.F.R. §§ 46.101-409. See Joan P. Porter, *The Federal Policy for the Protection of Human Subjects*, 13 IRB: A REVIEW OF HUMAN SUBJECTS RES. 8 (1991). This federal policy has been adopted by 16 federal agencies and departments and applies to research funded by or subject to regulation from any of these agencies and departments. See *id.* The regulations provide for Institutional Review Boards (IRBs) to review research proposals in order to determine, in part, whether the investigator has complied with informed consent requirements to adequately protect human subjects. See 45 C.F.R. § 46.109.

114. See 45 C.F.R. § 46.101.

115. See *id.* §§ 46.401-409 (Subpart D—Additional Protections for Children Involved as Subjects in Research).

116. See *id.* §§ 46.301-306 (Subpart C—Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects).

117. See *id.* §§ 46.201-211 (Subpart B—Additional Protections Pertaining to Research, Development, and Related Activities Involving Fetuses, Pregnant Women,

The Human Subjects Regulations do not apply to privately funded research. A second set of federal regulations, promulgated under the Federal Food, Drug, and Cosmetic Act,¹¹⁸ regulate privately funded human subjects research that is intended to introduce a new drug or medical device to the market.¹¹⁹ The investigational new drug regulations control the conduct of clinical trials.¹²⁰ The FDA regulations adopt parts of the Human Subjects Regulations, including a special section for protections pertaining to clinical investigations involving prisoners as subjects,¹²¹ but do not adopt the sections outlining special protections for pregnant women or fetuses. It has been through the issuance of FDA guidelines that the participation of women of "childbearing potential" in clinical trials, until recently, has been severely limited.¹²²

The combined regulatory impact of both DHHS and FDA regulations is significant: federal policy governs nearly all human subjects biomedical and behavioral drug research conducted in the United States. An examination of the historical development of federal policy follows in order to illuminate the barriers to the participation of women in clinical research and to place these barriers in historical context.

and Human In Vitro Fertilization).

118. 21 U.S.C. §§ 301-395 (1994).

119. See 21 C.F.R. §§ 50.1-48, 56.101-124, pt. 312 (1995).

120. See *id.* § 50.1 (providing that the regulations apply to "clinical investigations that support applications for research or marketing permits for products regulated by the [FDA]").

121. See *id.* §§ 50.40-48.

122. See FDA, U.S. DEPT OF HEALTH, EDUC., & WELFARE, GENERAL CONSIDERATIONS FOR THE CLINICAL EVALUATION OF DRUGS 15 (1977). However, the FDA announced on March 24, 1993 that it was lifting the ban on women of childbearing age participating in early drug trials in order to encourage study of the effects pharmaceuticals have on women. See Philip J. Hilts, *F.D.A. Ends Ban on Women in Drug Testing*, N.Y. TIMES, Mar. 25, 1993, at B8. Those companies who submit funding applications for clinical research trials that do not include sufficient numbers of women risk having their applications denied by the FDA. See *id.* In response to concerns for protection of the fetus, the FDA's guidelines set out that women participants must give informed consent that they are aware of fetal risks inherent in the study and are informed of the need for taking precautions against pregnancy while participating in the trial. See *id.* Thus for the FDA, "protection of the fetus" consists of assuring that there is and will be no fetus. The question remains as to whether women who are pregnant will be allowed to participate in FDA supported clinical trials that offer treatment for the woman's health. See generally Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs, 58 Fed. Reg. 39,406, 39,411 (1993) (advising that "[a]ppropriate precautions should be taken . . . to guard against inadvertent exposure of fetuses to . . . toxic agents").

A. The History of Regulating Human Subjects Research

During the early 19th century, clinical trials depended largely upon experimentation with African-American slave women.¹²³ Anesthesia was not available, and experiments often were repeated on these women to perfect methods.¹²⁴ It was only by using slave women that researchers and physicians were able to experiment with various medical procedures.¹²⁵ By the turn of the century, human research subjects were no longer slave women, but primarily prisoners and other institutionalized populations.¹²⁶ In fact, FDA officials estimate that until 1972, more than 90% of all investigational drugs were first tested on prisoners.¹²⁷

Spurred by abuses in the research community, protectionism arose, in part, because of a deeply felt need to control experimentation on humans. The public viewed experimentation as a threatening force rather than a gateway to better health. In 1949, the Nuremberg Code¹²⁸ set out ethical and legal standards for the conduct of human research aimed at protecting human research subjects from the types of experimentation practices used by the Nazis in World War II.¹²⁹ Despite codification of the Code, problems persisted, and regulations were slow to develop in the United States.¹³⁰

123. See Ruth B. Merkatz & Suzanne W. Junod, *Historical Background of Changes in FDA Policy on the Study and Evaluation of Drugs in Women*, 69 ACAD. MED. 703, 705 (1994).

124. See *id.*

125. See *id.*

126. See *id.*

127. *Id.* By 1979 this percentage dropped to less than 15%. *Id.*

128. See The Nuremberg Code (1949), reprinted in ROBERT J. LEVINE, *ETHICS AND REGULATION OF CLINICAL RESEARCH* 425 (2d ed. 1986) [hereinafter LEVINE] ("The voluntary consent of the human subject is absolutely essential."); see also 1 WOMEN AND HEALTH RESEARCH, *supra* note 3, at 37-38 (discussing the evolution of the Nuremberg Code).

129. At one of the Nuremberg Trials, numerous Nazi doctors were tried for war crimes, which included research atrocities. See ROBERT E. CONOT, *JUSTICE AT NUREMBERG* 286 n.* (1983). The Nuremberg judges, warning that experiments on humans must be "kept within reasonable well-defined bounds," developed a set of principles enumerating the conditions under which medical experimentation on humans is permissible. See LEVINE, *supra* note 128, at 425-26 (providing that research must be performed pursuant to informed, voluntary consent, that the risk imposed on the subject should be minimal and justified, and that either the subject or the examiner must be allowed to terminate the experiment at any time). Although long since expanded and modified, the Nuremberg Code embodies the basic legal, moral, and ethical limitations that protect human subjects of biomedical research. See Charles R. McCarthy, *Historical Background of Clinical Trials Involving Women and Minorities*, 69 ACAD. MED. 695, 696 (1994) (describing the Nuremberg Code as a "watershed event" in the history of medical ethics).

130. See McCarthy, *supra* note 129, at 696-97.

By 1953, the National Institutes of Health (NIH) established its first scientific review panel for research involving human subjects.¹³¹ The thalidomide and diethylstilbestrol (DES) tragedies intensified the drive to make pregnant women specific targets of protectionism.¹³² In part as a result of the thalidomide disaster, Congress passed legislation in 1962 granting the FDA a new charter for regulating drugs that required researchers to obtain information on safety and efficacy, as well as informed consent from research subjects.¹³³

It was not until 1966 that the U.S. Public Health Service issued its first policy for protection of human subjects, entitled Policy and Procedure Order 129.¹³⁴ This policy, which had no regulatory teeth, continued to evolve over the next five years.¹³⁵ It soon became obvious that existing policies to protect research subjects were wholly inadequate.

By 1973, revelation of research abuses in the Tuskegee Syphilis Study gained media and congressional attention.¹³⁶ During the next three years, DHEW and Congress would participate concurrently in the development of regulations to address human experimentation. In 1973, DHEW appointed a group to study "the development of special procedures for the use of incompetents or prisoners in biomedical research, compensation of persons injured in clinical investigations, and a general review of the legal/ethical responsibilities in the conduct of such research."¹³⁷ Incompetent persons and prisoners, *but not pregnant women*, were singled out for special protection.

Later that same year, DHEW published draft regulations and solicited public comment.¹³⁸ The draft proposed special protections for children, prisoners, and the mentally infirm,¹³⁹ but the health needs of pregnant women were not addressed.

131. See Merkatz & Junod, *supra* note 123, at 705.

132. See *id.* at 705-06.

133. See *id.* at 705. In 1962, Congress passed the Drug Amendments of 1962, Pub. L. No. 87-781, 76 Stat. 781 (codified as amended in scattered sections of 21 U.S.C.).

134. See McCarthy, *supra* note 129, at 696.

135. See *id.* (referring to the Public Health Service policy as "weak, vague, full of loopholes, and hortatory rather than regulatory").

136. From 1932-73, the U.S. Public Health Service supported a study of untreated syphilis, enrolling 400 African-American men, many of whom remained untreated even after antibiotics were available. 1 WOMEN AND HEALTH RESEARCH, *supra* note 3, at 34. It is worth noting that, in spite of all the attention about Tuskegee since then, it is rare to hear any concern about the women who were sexual partners of these men exposed unknowingly to syphilis.

137. 38 Fed. Reg. 27,882 (1973).

138. See *id.* at 31,738.

139. See *id.*

Pregnant women, however, were singled out for their role as "fetal containers" under special categories outlining guidelines for "research, development, and demonstration activities" on abortuses and the fetus in utero.¹⁴⁰ Not only did the proposal presuppose a maternal-fetal conflict, it deemed fetal protection a natural corollary to regulations protecting children as a special class:

The fetus. Respect for the dignity of human life must not be compromised whatever the age, circumstance, or expectation of life of the individual. Therefore, all appropriate procedures providing protection for children as subjects in biomedical research must be applied with equal rigor and with additional safeguards to the fetus.¹⁴¹

This high level of fetal protection was deemed consistent with *Roe v. Wade*,¹⁴² which had been decided earlier that year:

The recent decision of the Supreme Court on abortion does not nullify the ethical obligation to protect the developing fetus from avoidable harm. This obligation, along with the right of every woman to change her decision regarding abortion, requires that no experimental procedures entailing risk to the fetus be undertaken in anticipation of abortion.¹⁴³

As a form of supplemental protection for fetuses, the draft proposed that all research involving pregnant women would be reviewed by the Ethical Review Board, unless it was determined by the primary Review Committee that the fetus would not be exposed to risk.¹⁴⁴ The draft also proposed that "[r]ecruitment of pregnant subjects for research . . . must involve the institution's Protection Committee in a manner approved by the Board, to provide supplementary judgment."¹⁴⁵ The pregnant women's autonomous decisionmaking was further eroded by a paternal consent requirement:

The consent of both parents must be obtained for any research involving the fetus, any statutes to the contrary on consent for abortion notwithstanding. Both the mother and the father have an interest in the fetus, and legal responsibility for it, if it is born. Therefore, the father's consent must be

140. See *id.*

141. *Id.* at 31,742.

142. 410 U.S. 113 (1973).

143. 38 Fed. Reg. 31,742.

144. See *id.* However, the concept of a national Ethical Review Board never actually materialized because fetal research was such a "controversial political issue." See Gina Kolata, *U.S. Rule on Fetal Studies Hampers Research on AZT*, N.Y. TIMES, Aug. 25, 1991, at A20.

145. 38 Fed. Reg. 31,742 (emphasis added).

obtained for experimental procedures involving the fetus; consent of the father may be waived if his identity or whereabouts cannot be ascertained, or if he has been judged mentally incompetent.¹⁴⁶

DHEW proposed additional regulations that included protections for "activities involving pregnant women where the fetus may be adversely affected."¹⁴⁷ Board review would be required for all research activities that involved pregnant women, and research activities on pregnant women would be prohibited if the fetus could be harmed, unless the purpose of the research was to benefit that particular fetus.¹⁴⁸ The regulations further required paternal consent as well as maternal consent, if the father was "available and capable of participating in the consent process" for activities allowable under the regulations but which might affect the fetus.¹⁴⁹

As DHEW continued to refine its proposed regulations, Congress continued to investigate research abuses. Days of testimony detailed various research abuses, including the Tuskegee Syphilis Study,¹⁵⁰ forced sterilization cases in Montgomery, Alabama,¹⁵¹ and the use of Depo-Provera for unapproved purposes and without informed consent.¹⁵²

As a result of the heavy response to the draft regulations from DHEW grantee and contracting organizations,¹⁵³ and "coincidentally" with the passage of the National Research Act,¹⁵⁴ DHEW proposed further protective measures.¹⁵⁵ These protective measures were expressly developed to ensure that informed consent would be obtained from certain classes of research subjects deemed vulnerable.¹⁵⁶

Because "the majority of the more than 400 letters received on research with children, born and unborn, touched on one or

146. *Id.*

147. *Id.* at 31,747.

148. *See id.*

149. *Id.*

150. *See Quality of Health Care—Human Experimentation, 1973: Hearings Before the Subcomm. on Health of the Senate Comm. on Labor and Public Welfare*, 93d Cong., 1st Sess. 1187-88 (1973) (statement of Senator Edward Kennedy).

151. *See id.* at 1464-66 (questioning the adequacy of consent in federally sponsored sterilization programs).

152. *See id.* at 1314 (noting that Depo-Provera had been used in Alabama and Tennessee before it had been approved for general use).

153. *See* 38 Fed. Reg. 30,648 (1974) (noting that 450 such responses were received).

154. Pub. L. No. 93-348, 88 Stat. 342 (codified in scattered sections of 42 U.S.C.).

155. 39 Fed. Reg. 30,648.

156. *See id.* These were proposed as Subparts B-F.

more aspects of research with fetuses, abortuses, and pregnant women,¹⁵⁷ DHEW proposed the addition of a new and expanded Subpart entitled "Additional Protections Pertaining to Biomedical Research, Development, and Related Activities Involving Fetuses, Abortuses, Pregnant Women, and In Vitro Fertilization."¹⁵⁸ While many comments received by DHEW objected to the research on the fetus or the pregnant woman if the research might harm the fetus,¹⁵⁹ DHEW noted that the absence of such research "would seriously hamper the development of needed improvements in the health care of the pregnant woman, the fetus, and the newborn."¹⁶⁰

The draft regulation was also criticized for the paternal consent provision, because a paternal consent clause: (1) could provide men with a veto to health care needed by the woman or fetus, even though the man had no marital obligations, (2) could delay necessary medical treatment, and (3) failed to address the validity of consent by pregnant minors.¹⁶¹ As a result of the comments, DHEW altered the paternal consent provision by requiring paternal consent only if the activity was not responding to the health needs of the woman and the father was reasonably available.¹⁶² As DHEW issued these proposed regulations, the charter of the National Commission for the Protection of Human Subjects was approved by the Secretary of DHEW on August 23, 1974.¹⁶³

In its mandate, the Commission was charged, in part, with identifying informed consent requirements for children, prisoners, and the institutionalized mentally ill—populations who were considered particularly "vulnerable" to informed consent abuses and coercion.¹⁶⁴ The Commission was also charged with investigating research involving living fetuses.¹⁶⁵ Interestingly, women who had been victimized by forced sterilization, Depo-Provera, and other abuses were not designated by Congress as a group requiring special informed consent protection.

157. *Id.* at 30,649.

158. *Id.* at 30,653.

159. *See id.* at 30,649.

160. *Id.* Some comments criticized the limitation on research activities involving pregnant women to those activities that did not adversely affect the fetus, except where the primary purpose of the activity was to benefit the fetus. *See id.* at 30,651. These critics recommended exceptions for research necessary to meet the health needs of the mother and participation in "research aimed at improvement of methods of abortion, birth control, and genetic intervention." *Id.*

161. *See id.*

162. *See id.*

163. *See* 39 Fed. Reg. 32,172 (1974).

164. *See id.*

165. *See id.*

The Commission held public meetings and had special reports and papers prepared for its review.¹⁶⁶ It made sixteen recommendations regarding research involving fetuses.¹⁶⁷ Two of the recommendations involved pregnant women:

2. *Therapeutic research directed toward the pregnant woman* may be conducted or supported, and should be encouraged, by the Secretary, DHEW, provided such research (a) has been evaluated for possible impact on the fetus, (b) will place the fetus at risk to the minimum extent consistent with meeting the health needs of the pregnant woman, (c) has been approved by existing review procedures with adequate provision for the monitoring of the consent process, and (d) the pregnant woman has given her informed consent. (Adopted unanimously.)

3. *Nontherapeutic research directed toward the pregnant woman* may be conducted or supported by the Secretary, DHEW, provided such research (a) has been evaluated for possible impact on the fetus, (b) will impose minimal or no risk to the well-being of the fetus, (c) has been approved by existing review procedures with adequate provision for the monitoring of the consent process, (d) special care has been taken to assure that the woman has been fully informed regarding possible impact on the fetus, and (e) the woman has given informed consent. (Adopted unanimously.)

It is further provided that nontherapeutic research directed at the pregnant woman may be conducted or supported (f) only if the father has not objected, both where abortion is not at issue (adopted by a vote of 8 to 1) and where an abortion is anticipated (adopted by a vote of 5 to 4).¹⁶⁸

166. See NATIONAL COMM'N FOR THE PROTECTION OF HUMAN SUBJECTS OF BIOMEDICAL & BEHAVIORAL RESEARCH, U.S. DEPT OF HEALTH, EDUC., & WELFARE, RESEARCH ON THE FETUS: REPORT AND RECOMMENDATIONS (1975) [hereinafter 1975 REPORT]; NATIONAL COMM'N FOR THE PROTECTION OF HUMAN SUBJECTS OF BIOMEDICAL & BEHAVIOR RESEARCH, U.S. DEPT OF HEALTH, EDUC., & WELFARE, RESEARCH ON THE FETUS: APPENDIX (1975).

Other publications from the National Commission for the Protection of Human Subject of Biomedical and Behavioral Research include: NATIONAL COMM'N FOR THE PROTECTION OF HUMAN SUBJECTS OF BIOMEDICAL & BEHAVIORAL RESEARCH, U.S. DEPT OF HEALTH, EDUC., & WELFARE, THE BELMONT REPORT: ETHICAL PRINCIPLES AND GUIDELINES FOR THE PROTECTION OF HUMAN SUBJECTS OF RESEARCH (1978); NATIONAL COMM'N FOR THE PROTECTION OF HUMAN SUBJECTS OF BIOMEDICAL & BEHAVIORAL RESEARCH, U.S. DEPT OF HEALTH, EDUC., & WELFARE, THE BELMONT REPORT: ETHICAL PRINCIPLES AND GUIDELINES FOR THE PROTECTION OF HUMAN SUBJECTS OF RESEARCH, APPENDIX VOLUME I (1978); NATIONAL COMM'N FOR THE PROTECTION OF HUMAN SUBJECTS OF BIOMEDICAL & BEHAVIORAL RESEARCH, U.S. DEPT OF HEALTH, EDUC., & WELFARE, THE BELMONT REPORT: ETHICAL PRINCIPLES AND GUIDELINES FOR THE PROTECTION OF HUMAN SUBJECTS OF RESEARCH, APPENDIX VOLUME II (1978).

167. See 1975 REPORT, *supra* note 166, at 73-76.

168. *Id.* at 73.

However, the Commission *did not recommend* paternal consent for therapeutic research directed toward the health needs of the pregnant woman.

DHEW issued the final regulations on August 8, 1975,¹⁶⁹ thereby officially extending "additional protections" to research subjects of biomedical research, development, and related activities involving, among other groups, fetuses, pregnant women, and in vitro fertilization.¹⁷⁰ DHEW noted that the Commission drew distinctions between research directed toward the pregnant woman and research directed at the fetus in utero.¹⁷¹ The Department found this distinction "useful" and adopted it.¹⁷² In commenting on the Commission's recommendations, DHEW agreed:

The Commission considered that the woman's right to health care is preeminent, and recommended essentially no restrictions on research directed toward the health care of the pregnant woman, so long as the risks to her fetus are minimized as much as possible consistent with meeting her health needs, and provided that she is fully advised of the risks to herself and her fetus.¹⁷³

As for research directed toward the pregnant woman, but not for the purpose of meeting her health needs, DHEW found that there seemed to be "general agreement that such research should be permitted only if it imposes minimal or no risk to the fetus."¹⁷⁴ Perhaps most significantly, DHEW admitted that disagreement existed among the commentaries with respect to paternal consent: "The Department has considered with care the various arguments with respect to consent other than the pregnant woman's for nontherapeutic research involving the pregnant woman, and concludes that such consent should be obtained except where such research involves the health needs of the woman."¹⁷⁵

It further noted that, in a number of instances, the Commission recommended that research should be permitted if the mother has consented and the father has not objected.¹⁷⁶ The Department concluded that "implementation of a provision for

169. Protection of Human Subjects, 40 Fed. Reg. 33,526 (1975) (codified as amended at 45 C.F.R. §§ 46.101-409).

170. See *id.* at 33,528-30 (codified as amended at 45 C.F.R. §§ 46.201-.211).

171. See *id.* at 33,527.

172. *Id.*

173. *Id.*

174. See *id.*

175. *Id.*

176. See *id.*

absence of objection might present serious problems."¹⁷⁷ Because the absence of objection can be proven best by requesting consent, "the Department . . . retained the requirement for paternal consent when the father's identity and whereabouts can reasonably be ascertained, and if he is reasonably available."¹⁷⁸ The Subpart B regulations¹⁷⁹ were finalized and remain essentially unaltered.¹⁸⁰

The protections provided in Subpart B are in addition to and supplement the general provisions of Subpart A.¹⁸¹ Under Subpart B, no research activities on pregnant women or fetuses may be undertaken unless animal studies and studies on non-pregnant individuals have been completed first.¹⁸² The risk posed to the fetus by biomedical research must be minimal, except when the research activity is designed to meet the health needs of the particular mother or fetus.¹⁸³ Invariably, the risk to the fetus must always be the "least possible risk for achieving the objectives of the activity."¹⁸⁴ Individuals engaged in the activity may not participate in the decisionmaking regarding terminating the pregnancy, offer inducements to coerce the termination, or alter the procedures for terminating the pregnancy in ways that increase the minimal risk to the pregnant woman or fetus.¹⁸⁵

Section 46.207 of Subpart B specifically regulates research activities "directed toward pregnant women as subjects" and severely limits the participation of pregnant women in biomedical research and development by creating a two-tiered test for participation.¹⁸⁶ A pregnant woman may be involved in research only if: "(1) The purpose of the activity is to meet the health needs of the mother *and* the fetus will be placed at risk only to the minimum extent necessary to meet such needs, *or* (2) the risk to the fetus is minimal."¹⁸⁷

177. *Id.*

178. *Id.*

179. 45 C.F.R. §§ 46.201-211.

180. During 1994-95, a Human Subject Regulations Drafting Committee, established by the Public Health Service, considered amending Subpart B in accordance, in part, with the recommendations of the Institute of Medicine's Committee on the Ethical and Legal Issues Relating to the Inclusion of Women in Clinical Studies. Refer to Part V *infra*. To date, no final action has been taken on the Drafting Committee's recommendation.

181. See generally Porter, *supra* note 113, at 8-9 (discussing the history of Subpart A).

182. See 45 C.F.R. § 46.206(a)(1).

183. See *id.* § 46.206(a)(2).

184. *Id.*

185. See *id.* § 46.206(a)(3)-(4), (b).

186. *Id.* § 46.207.

187. *Id.* § 46.207(a) (emphasis added). "Minimal risk" is not specifically defined

If the research activity survives this initial threshold test for participation, the activity then may be conducted only if the mother *and father*¹⁸⁸ are legally competent and have given their informed consent after receiving complete information regarding the possible impact on the fetus.¹⁸⁹ The reputed father's informed consent is not necessary if: "(1) The purpose of the activity is to meet the health needs of the mother; (2) his identity or whereabouts cannot reasonably be ascertained; (3) he is not reasonably available; or (4) the pregnancy resulted from rape."¹⁹⁰

The concept of "health needs of the mother" is not defined under the regulations, and as a practical matter, it may be very difficult to sort out when a proposed activity is to meet the health needs of the mother, fetus, or both. This lack of clarity may be quite significant because section 46.208 sets out different standards of paternal consent for activities directed toward fetuses in utero.¹⁹¹ Under these circumstances, the reputed father's consent is required unless "(1) His identity or whereabouts cannot reasonably be ascertained, (2) he is not

in Subpart B, but in the general provisions it is defined to mean risks not greater, considering probability and magnitude, "than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests." *Id.* § 46.102(i).

188. The term "father" is not defined under the regulations. In fact, it may be totally premature to label a sexual partner a father in this context. "Parental rights do not spring full-blown from the biological connection between parent and child. They require relationships more enduring. The mother carries and bears the child, and in this sense her parental relationship is clear. The validity of the father's parental claims must be gauged by other measures." *Caban v. Mohammed*, 441 U.S. 380, 397 (1979) (Stewart, J., dissenting).

Some of the measures courts use to analyze paternal rights in respect to children (not fetuses) include marital status, paternity testing and paternal acknowledgment, the degree of participation in the child's life, and the best interest of the child. *See, e.g., Sider v. Sider*, 639 A.2d 1076, 1083-86 (Md. 1994) (listing as factors that must be balanced in a custody case the establishment of paternity: availability of a family unit, the child's relationship with the parties, and the best interest of the child); *In re J.W.T.*, 872 S.W.2d 189, 195 (Tex. 1994) (analyzing a biological father's paternal acknowledgment and commitment to parental duties to determine his parental rights). When the family law of the various states considers paternal claims over rearing of existing children, father may be defined very broadly. For example, under New York State law, in addition to men listed in the state's putative father directory, notice of an adoption proceeding must be given to several other classes of possible fathers of children born out of wedlock, including those the mother identifies as the father in a sworn written statement. *See Lehr v. Robertson*, 463 U.S. 248, 251 (1983).

189. *See* 45 C.F.R. § 46.207(b).

190. *See id.*

191. *See id.* § 46.208(a). Experiments on the fetus in utero are limited to research to meet the needs of the fetus or research in which the risk is minimal and the purpose is the "development of important biomedical knowledge which cannot be obtained by other means." *Id.*

reasonably available, or (3) the pregnancy resulted from rape."¹⁹² These artificial distinctions in this context result in regulatory frustration and the perpetuation of the presumption that a pregnant woman cannot decide what is best either for her or her fetus.¹⁹³

It is incongruous that the paternal consent requirements in Subpart B¹⁹⁴ have remained in place while DHHS regulations on research involving children¹⁹⁵ only require the permission of one parent when such research poses either no greater than minimal risk or the prospect of direct benefit to the child.¹⁹⁶ Although the permission of both parents generally is required for all other forms of research on children, the consent of only one parent will be sufficient if the other parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent maintains legal responsibility for the care and custody of the child.¹⁹⁷ Subpart B and its "special" treatment of pregnant women would become symbolic of the regulatory barriers to research that still remain.

B. A New Era for Inclusion of Women in Clinical Research

The changing view of participation in clinical trials as a benefit rather than a burden provided the momentum of the

192. *Id.* § 46.208(b).

193. For example, consider the ACTG 076 trial, "A Phase III Randomized Placebo-Controlled Trial to Evaluate the Efficacy, Safety and Tolerance of Zidovudine [ZDV] for the Prevention of Maternal-Fetal HIV Transmission." The goal of the trial was to measure the effect of ZDV in reducing vertical transmission from mother to fetus. The inclusion criteria for the study eliminated those women with CD4 cell counts below 200, those women most sick with AIDS. In addition, there was no planned long-term follow up for the women who did participate in the trial. Thus, in a clinical trial that allowed for the study of the effects of ZDV in pregnant women, the focus actually appeared to be on the fetus. Characterized in this way then, paternal consent was required for research on the fetus (and the pregnant woman) absent the regulatory exceptions found in 45 C.F.R. § 46.208.

194. 45 C.F.R. §§ 46.207(b), 46.208(b), 46.209(d).

195. *Id.* §§ 46.401-409.

196. *See id.* §§ 46.404, 46.405, 46.408. Pursuant to § 46.408, the permission of both parents is required for research involving greater than minimal risk and no prospect of direct benefit, but likely to yield generalizable knowledge about the subject's disorder or condition. *See id.* § 46.408(b). Research not otherwise approvable that presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children also requires permission from both parents. *See id.* The Commission did not explain its inconsistency in position with respect to parental consent. It is worth noting, however, that the Commission studied fetal protection under political pressure and, as they admitted, at a hurried pace. *See* 1975 REPORT, *supra* note 166, at 61 (noting that the Commission was "placed under severe limitations of time by its Congressional mandate").

197. 45 C.F.R. § 46.408(b).

movement toward increased inclusion of women in clinical research. Beginning with AIDS research, the focus of public attention regarding clinical trials turned toward access rather than protection.¹⁹⁸ As AIDS activists cried out for improved access, the public began to realize the numerous advantages afforded to research participants.¹⁹⁹ These include possible therapeutic advantages when other treatments are inadequate, close monitoring of the disease, attention for other ailments, superior physicians, labs, and testing, more contact with the providers, remunerations, and contributions to society.²⁰⁰

Exclusionary gender policies and regulatory barriers to research have consequently fallen prey to serious scrutiny. In 1983, the U.S. Public Health Service appointed a task force to address women's health issues. As noted earlier, its 1985 Report concluded that there were significant deficiencies in biomedical research addressing women's health needs: "The historical lack of research focus on women's health concerns has compromised the quality of health information available to women as well as the health care they receive."²⁰¹ The NIH would now have to take action.

1. *NIH Policy: From Encouragement to Requirement.* In 1986, NIH issued and implemented guidelines urging funding applicants to include women in clinical research and requiring a clear rationale if women were to be excluded.²⁰² In 1990, a General Accounting Office (GAO) report²⁰³ confirmed that women were not sufficiently represented in clinical trials. More specifically, the GAO found that: the policy on women had not been well-communicated or understood within NIH or the research community; there were inconsistencies in how the policy had been applied in key stages of the grant review process; NIH officials had taken little action to encourage researchers to analyze study results by gender; and NIH had no way to measure the policy's impact on its research, including its effect on

198. See Merton, *supra* note 42, at 377 (noting the desire of research subjects to receive access to experimental drugs and therapies).

199. See *id.* (reporting the battle cry of AIDS advocates: "[T]rials are treatment").

200. See *id.* at 379.

201. 1 WOMEN AND HEALTH RESEARCH, *supra* note 3, at 43 (citing Task Force Report, *supra* note 1).

202. See U.S. Dep't of Health & Human Servs., 15 NIH GUIDE FOR GRANTS AND CONTRACTS 1 (1986). The 1986 NIH policy applied to extramural research projects only and not to NIH's own intramural research projects. See *id.* at 1.

203. See U.S. GEN. ACCOUNTING OFFICE, NATIONAL INSTITUTES OF HEALTH: PROBLEMS IN IMPLEMENTING POLICY ON WOMEN IN STUDY POPULATIONS (1990).

the demographic composition of study populations.²⁰⁴

Consequently, by the fall of 1990, NIH announced criteria for the awarding of research grants, through a series of memoranda and notices, that required the inclusion of women and minorities in NIH-supported intramural and extramural research.²⁰⁵ The new policy distinguished between extramural grants awarded to institutions and individuals outside of NIH and intramural grants awarded to investigators at the NIH. Extramural grants awarded to conduct human subjects research were required to include minorities as well as both genders, except in those cases where the grant applicant could provide "compelling justification" for exclusion.²⁰⁶ Compelling justification was defined as "strong scientific or practical reasons for exclusion,"²⁰⁷ including an "unacceptable risk for women of childbearing age."²⁰⁸ NIH intramural researchers could exclude women where there was a "clear rationale" for doing so,²⁰⁹ including where involvement of pregnant women "may expose the fetus to undue risks."²¹⁰ This policy remained in effect until June 10, 1993, when the National Institutes of Health Revitalization Act of 1993²¹¹ was signed into law.²¹²

The NIH Revitalization Act mandates that the Director of NIH "ensure" that both women and minority groups be included in both intramural and extramural research funded by NIH.²¹³

204. See *id.* at summary (statement of Mark V. Nadel, Associate Director, GAO).

205. NATIONAL INSTITUTES OF HEALTH, INSTRUCTION AND INFORMATION MEMORANDUM OER 90-5: NIH GUIDANCE ON THE INCLUSION OF MINORITIES AND WOMEN IN CLINICAL RESEARCH STUDY POPULATIONS (1990) (on file with the *Houston Law Review*).

206. *Id.* at 1.

207. The Memorandum OER 90-5 provided that acceptable justifications may include research on a "predominantly or exclusively . . . male condition," certain pilot and feasibility studies in which "[g]ender differences may not be germane," research in an area that "has already been extensively studied in women," and in certain instances, studies that would be "prohibitively expensive." *Id.* at 30.

208. *Id.*

209. Memorandum from Edward Rall, Deputy Director of Intramural Research, National Institutes of Health, *Policy on Inclusion of Women in Study Population* (Aug. 1, 1990) (on file with the *Houston Law Review*).

210. *Id.*

211. Pub. L. No. 103-43, 107 Stat. 122 (1993) (codified as amended in scattered sections of 42 U.S.C.).

212. Legislation to mandate the inclusion of women in clinical research also was proposed during the 1991-92 session of Congress. See LAURENCE & WEINHOUSE, *supra* note 10, at 68 (discussing the NIH Revitalization Amendments of 1991). The legislation passed both the House of Representatives and the Senate, but was vetoed by President Bush because of controversial provisions that lifted the moratorium on federally funded fetal tissue transplantation research. See *id.* The Revitalization Act of 1993 was signed by President Clinton and became law on June 10, 1993. See *id.*

213. Pub. L. No. 103-43, sec. 131, § 429B(a)(1)(A), 107 Stat. 122, 133. In addition, the Act statutorily authorized the Office on Women's Health within the Office

On March 28, 1994, NIH issued guidelines pursuant to the Act that strengthened its prior policy on inclusion in several respects.²¹⁴ Specifically, they:

- define clinical research to include all research involving human subjects;²¹⁵
- direct that women and members of minority subpopulations be included in all human subjects research;²¹⁶
- require inclusion of women and minorities and their subpopulations in Phase III clinical trials such that valid analyses of differences in intervention effect can be accomplished;²¹⁷
- promote development of outreach programs to recruit women and minorities and their subpopulations into clinical studies;²¹⁸ and

of the Director of NIH, *see id.* § 486(o), 107 Stat. at 136; required NIH to establish internal and external committees to advise it on issues in women's health research, including gender differences in clinical drug trials and disease etiology, course, and treatment, *see id.* § 486(d)(4)(A), 107 Stat. at 137; required NIH to determine the extent of women's representation among senior physicians and scientists conducting NIH-supported research and to carry out activities to increase the extent of such representation, *see id.* § 486(e), 107 Stat. at 138; and finally, mandated the establishment of a national data system and clearinghouse on research of women's health, *see id.* § 486A(a), (b) 107 Stat. at 138.

Under the Act, the entire scientific community shares the responsibility for fulfilling the intent of the law and ensuring that the results of research are broadly applicable. Principal investigators assess the theoretical or scientific links between gender, race, ethnicity, and their topic of study in preparing their applications. *See* 59 Fed. Reg. 14,508, 14,510 (1994). Institutional Review Boards review NIH protocols in terms of the NIH inclusion policy during their review for protection of human subjects. *See id.* Peer review groups include a scientific and technical merit evaluation of the inclusion plan and assign appropriate scores for the award of grants. *See id.* Finally, the advisory council or board of each institute or center prepares reports describing the manner in which the institute or center has complied with the provisions of the statute. *See id.*; *see also* NATIONAL INSTITUTES OF HEALTH, QUESTIONS AND ANSWERS CONCERNING THE 1994 NIH GUIDELINES ON THE INCLUSION OF WOMEN AND MINORITIES AS SUBJECTS IN CLINICAL RESEARCH 8-13 (1994) [hereinafter NIH Q & A] (providing information to the scientific community concerning the scope of the policy, applicable definitions of "minorities," and compliance regulations).

214. 59 Fed. Reg. 14,508.

215. *See id.*

216. *See id.* Although it is very significant that minorities and their subpopulations are recruited into clinical studies, this analysis is limited to the including of women. For a discussion of the importance of inclusion minorities and subpopulations, *see generally* 1 WOMEN AND HEALTH RESEARCH, *supra* note 3, at 114-19; Dresser, *supra* note 12, at 24.

217. *See* 59 Fed. Reg. 14,508.

218. *See id.* In addition to numerous educational programs for the scientific community, ORWH has prepared an Outreach Notebook for the NIH Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research. *See* NATIONAL INSTITUTES OF HEALTH, OUTREACH NOTEBOOK FOR THE NIH GUIDELINES ON INCLUSION OF WOMEN AND MINORITIES AS SUBJECTS IN CLINICAL RESEARCH (1994). It has

- do not allow cost as an acceptable reason for excluding these groups in clinical trials.²¹⁹

All biomedical and behavioral research, including small scale (*i.e.*, Phase I and II), exploratory, or observational studies, as well as large scale studies, falls within the definition of "clinical research."²²⁰ The policy extends to all research involving the use of human organs, tissues, and body fluids from living individuals and to graphic, written, or recorded information derived from living individuals.²²¹ Even research that is exempt from Institutional Review Board (IRB) review is *not* exempt from NIH policies on the inclusion of both genders in study populations.²²²

Although the inclusion of women is required in all phases of clinical research, it is only for Phase III clinical trials that the guidelines require the performance of valid analysis²²³ of clinically important gender differences in response to the intervention.²²⁴ The NIH defines a clinical trial as

a broadly based prospective Phase III clinical investigation, usually involving several hundred or more human subjects, for the purpose of evaluating an experimental intervention in comparison with a standard or control intervention or comparing two or more existing treatments. . . . The definition includes pharmacologic, non-pharmacologic, and behavioral interventions given for disease prevention, prophylaxis, diagnosis,

also held public hearings and published its report on improving the recruitment and retention of women in clinical trials. OFFICE OF RESEARCH ON WOMEN'S HEALTH, NATIONAL INSTITUTES OF HEALTH, RECRUITMENT AND RETENTION OF WOMEN IN CLINICAL STUDIES (1994).

219. See 59 Fed. Reg. 14,508.

220. NIH Q & A, *supra* note 213, at 10. The policy is based on the definition for human subjects in the federal regulations: "a living individual about whom an investigator (whether professional or student) conducting research obtains: (1) Data through intervention or interaction with the individual, or (2) Identifiable private information." 45 C.F.R. § 46.102(f).

221. See NIH Q & A, *supra* note 213, at 11; see also Judith LaRosa et al., *Including Women and Minorities in Clinical Research*, 4 APPLIED CLINICAL TRIALS 31, 32 (1995) (noting that the "rationale for such a broad definition [of research] is to detect trends of potential gender, racial, and ethnic differences by obtaining the greatest possible amount of information from the earliest stages of scientific inquiry").

222. See NIH Q & A, *supra* note 213, at 10. The guidelines, however, do not require IRBs to review research that is exempt. For example, pursuant to 45 C.F.R. § 46.101(b)(3), research involving the use of educational tests, certain research and demonstration projects, and food quality studies are exempt from IRB review. See *id.*

223. Valid analysis is defined as an assessment that will, on average, provide the correct estimate of the difference in outcomes between the groups of subjects. See NIH Q & A, *supra* note 213, at 13.

224. See 59 Fed. Reg. 14,508.

or therapy. Community trials and other population-based intervention trials are also included.²²⁵

The objective of such investigation is "to provide evidence leading to a scientific basis for consideration of a change in health policy or standard of care."²²⁶ This definition is much broader than the FDA definition of Phase III clinical trials, which focuses primarily on clinical investigation of drugs, vaccines, and biological and medical devices.²²⁷

In designing a Phase III clinical trial, the principal investigator must comply with the following standards for valid analysis of gender differences: if the data strongly indicate the existence of significant differences or are inconclusive about potential differences, the principal investigator will be required to include sufficient and appropriate recruitment of both genders in the study design.²²⁸ If the data generated from earlier studies strongly support no significant differences, then inclusion is not required, but is "still strongly encouraged."²²⁹

Pursuant to the Act, women may be excluded from all phases of a clinical research project if inclusion is "inappropriate with respect to the health of the subjects," is "inappropriate with respect to the purpose of the research," or is "inappropriate under such other circumstances as the Director of NIH may designate."²³⁰ By example, NIH has stated that

225. *Id.* at 14,511.

226. *Id.*

227. *See* NIH Q & A, *supra* note 213, at 11 (citing the FDA definition of Phase III trials as only expanded, controlled, and uncontrolled trials). Phase III trials are performed after preliminary evidence suggesting effectiveness of the drug has been obtained. *See* 21 C.F.R. § 312.21. They are intended to gather the additional information about the effectiveness and safety required to evaluate overall benefit-risk relationship of the drug and to provide an adequate basis for physician labeling. *See id.*

228. *See* NIH Q & A, *supra* note 213, at 12-13. It is only in the case where data strongly indicates the existence of significant differences that the trial must be designed with high statistical power of the intervention effect in the separate genders. *See id.* For example, if men and women are thought to respond differently to an intervention, then the Phase III trial must be designed to answer two separate primary questions, one for men and the other for women, with adequate sample size for each. *See id.* at 12.

229. *Id.* at 13. Thus, it may be to the benefit of researchers to collect data by gender in the early phases of clinical research because gender analysis need not be performed nor will gender be required as subject selection criteria if the data strongly support no significant differences of clinical or public health importance in intervention effect between genders.

230. National Institutes of Health Revitalization Act of 1993, Pub. L. No. 103-43 sec. 131, § 492B(b), 107 Stat. 122, 134. NIH has delineated a number of examples of possible acceptable justifications, including the following instances:

- One gender (male or female) may be excluded from a study because:
 - inclusion of these individuals would be inappropriate with

"experimental procedures/treatments . . . [that pose an] unacceptable risk for women of childbearing potential" may be a possible acceptable justification for excluding women from a clinical study.²³¹ This justification is carried over from earlier NIH policy,²³² in spite of the fact that the guidelines expressly recognize that "[w]omen of childbearing potential should not be routinely excluded from participation in clinical research."²³³

Although "inappropriateness" may sometimes justify exclusion, the Act clearly states that, contrary to former NIH policy, cost will *not* be deemed an acceptable reason for excluding women in clinical trials.²³⁴ Many researchers and

respect to their health (e.g., experimental procedures/treatments present unacceptable risk for women of childbearing potential. It should be noted however, that women of childbearing potential should not be routinely excluded.);

- the research question addressed is relevant to only one gender; or
- evidence from prior research strongly demonstrates no difference between genders; or
- sufficient data already exist with regard to the outcome of comparable studies in the excluded gender, and duplication is not needed in this study.
- One gender is excluded or severely limited because the purpose of the research constrains the applicant's selection of study subjects by gender (e.g., uniquely valuable stored specimens or existing datasets are single gender; very small numbers of subjects are involved; or overriding factors dictate selection of subjects, such as matching of transplant recipients, or availability of rare surgical specimens.)
- Gender representation of specimens or existing datasets cannot be accurately determined, e.g., pooled blood samples, stored specimens, or datasets with incomplete gender documentation are used, AND this does not compromise the scientific objectives of the research.
- The scientific question requires the use of the same or a comparable study population as that used in an earlier study and the potential gain in scientific knowledge outweighs the imbalance in the study population.
- Research is proposed with a pre-defined unique but underrepresented population (e.g., an extensive registry of patients with the condition of interest) and would not be feasible if a different sample were used.

Each of these justifications would be evaluated by Initial Review Groups in the context of the specific scientific goals and issues being addressed. Depending on the details, these justifications may or may not be considered adequate and compelling.

NIH Q & A, *supra* note 213, at 25-26.

231. *Id.* at 25.

232. Refer to notes 205-12 *supra* and accompanying text.

233. 59 Fed. Reg. 14,509. On September 15, 1995, the Centers for Disease Control and Prevention (CDC) published its own Policy on the Inclusion of Women and Racial and Ethnic Minorities in Externally Awarded Research. See 60 Fed. Reg. 47,947 (1995). It states that "women of childbearing potential should also not be routinely and/or arbitrarily excluded from participation even though there are ethical/risk issues to consider for inclusion and exclusion." *Id.* at 47,949.

234. See Pub. L. No. 103-43, sec. 131 § 429B(d)(2)(A)(i), 107 Stat. 122, 134. In

policymakers have expressed concern about the implications of this provision.²³⁵ If priority goes to costly "inclusive" projects, critics have warned the NIH will be limited to funding fewer studies.²³⁶ Moreover, experts have warned that "if the act is too rigidly interpreted, it will make costly and unreasonable demands on the scientific research process and impede the implementation of its noble goal."²³⁷

On March 28, 1995, the one year comment period to respond to the NIH guidelines ended.²³⁸ A number of respondents expressed serious concern about the cost of expanding clinical trials to meet the inclusion requirements, particularly with respect to minority groups and their subpopulations.²³⁹ The statutory mandate, however, was explicit that "'cost is not a permissible consideration'" and does not authorize the NIH guidelines to provide otherwise.²⁴⁰ The more germane question may well be "What is the cost of not including women and minorities?"²⁴¹

2. *FDA Policy: From Exclusion to Encouragement.* The Food and Drug Administration (FDA) regulates privately funded

addition, cost is not an acceptable reason for exclusion in other types of clinical research except when the study would duplicate data from other sources. See 59 Fed. Reg. 14,509.

235. See, e.g., Sally L. Satel, *Science by Quota*, NEW REPUBLIC, Feb. 27, 1995, at 14, 14 (arguing that the regulations inappropriately allow "politicians to dictate how scientists must do their work" and that "[b]y the time a diligent researcher has ensured that adequate numbers of minorities participate [in studies], . . . the size and price tag of the grant proposal will skyrocket").

236. See *id.* at 16. See generally Marcia Angell, *Caring for Women's Health—What is the Problem?*, 329 NEW ENG. J. MED. 271, 271-72 (1993) (concluding that "[l]yes, women should be included more often in clinical trials, but not according to a formula that would make clinical trials more difficult than ever and probably be counterproductive in terms of learning about differential effects in women"); J. Claude Bennett, *Inclusion of Women in Clinical Trials—Policies for Population Subgroups*, 329 NEW ENG. J. MED. 288, 291 (1993) (maintaining that the "global solution" of the NIH Revitalization Act "cannot provide the answers to complex and varied questions about the effects of therapy on women").

237. 1 WOMEN AND HEALTH RESEARCH, *supra* note 3, at 3.

238. Most of the public comments received focused on the inclusion requirements for minority groups and their subpopulations, expressing concern about the difficulties in recruiting sufficient numbers, particularly in certain geographic regions. See Eugene Hayunga, U.S. DEP'T OF HEALTH & HUMAN SERVS., NIH POLICY AND GUIDELINES ON THE INCLUSION OF WOMEN (AND MINORITIES) AS SUBJECTS IN CLINICAL RESEARCH 4-5 (1995) (unpublished document) (on file with the *Houston Law Review*). While some concerns resulted from a misunderstanding of the requirement, others reflected the need for enhanced outreach activities and improved scientific collaboration. See *id.* at 4.

239. See *id.*

240. *Id.*

241. *Id.*

human subjects research that is intended to introduce a new drug or medical device to the market.²⁴² The FDA's policy on the inclusion of women in clinical trials is set forth in guidelines. These guidelines are not mandatory interpretations of FDA regulations, but rather "advisory opinions on an acceptable approach to meeting regulatory requirements, and research begun in good faith under such guidelines will be accepted by the Agency for review purposes unless the guideline (or the relevant portion of it) has been formally rescinded for valid health reasons."²⁴³

In its 1977 Guidelines, the FDA largely excluded women of childbearing potential from clinical trials:

In general, women of childbearing potential should be excluded from the earliest dose ranging studies. If adequate information on efficacy and relative safety has been amassed during Phase II, women of childbearing potential may be included in further studies provided Segment II and the female part of Segment I of the FDA Animal Reproduction Guidelines have been completed. All three Segments should be completed before large-scale clinical trials are initiated in women of childbearing potential.²⁴⁴

Although the 1977 FDA Guidelines largely excluded women from clinical trials, they did provide for three exceptional circumstances. Women of childbearing potential could undergo experimental drug testing if: (1) the purpose of the drug was to save or prolong life, (2) the drug belonged to a class of compounds for which teratogenic potential had already been established in animals, or (3) institutionalization of the woman had allowed investigators to verify that she was not pregnant.²⁴⁵

What is noteworthy in these guidelines is the language used both to "protect" and exclude women from clinical trials. Women of childbearing potential "may" be included if prior

242. See 21 U.S.C. §§ 351-360.

243. FDA, U.S. DEPT OF HEALTH, EDUC., & WELFARE, GENERAL CONSIDERATIONS FOR THE CLINICAL EVALUATION OF DRUGS 5 (1977) [hereinafter 1977 GUIDELINES].

A woman of childbearing potential is defined as a premenopausal female capable of becoming pregnant. This includes women on oral, injectable, or mechanical contraception; women who are single; [and] women whose husbands have been vasectomized or whose husbands have received or are utilizing mechanical contraceptive devices. Women in certain institutions, e.g., prisons [sic], although of childbearing potential, could be considered as not in the appropriate environment to become pregnant during the administration of an investigational drug. However, women in mental institutions could become pregnant.

Id. at 15.

244. *Id.*

245. See *id.*

animal studies have been completed. Also, all three segments "should" be completed before allowing women of childbearing potential to participate. In fact, prior animal reproduction studies are not required prior to Phase II and Phase III clinical trials, and FDA regulations stipulate that nonclinical studies are to be performed "as appropriate" for reproductive and fetal effects.²⁴⁶ The FDA allows drug manufacturers to market drugs without reproductive testing, as long as notice of this fact is included in the product label.²⁴⁷

The 1977 Guidelines briefly addressed the FDA's position on male reproductive effects:

Where testicular abnormalities or abnormalities of spermatogenesis have occurred in experimental animals or where chromosomal abnormalities are anticipated (e.g., alkylating agents), the criteria for inclusion of males in Phase I, II and III depend upon the nature of the abnormalities, the dosage at which they occurred, the disease being treated, the importance of the drug, and the duration of the drug administration. In some cases, special written consent forms, even in Phases III, may be required.²⁴⁸

What is noteworthy about these earlier guidelines is the risk/benefit approach for inclusion of males, even when male reproductive abnormalities may result from the drug. Whereas women of childbearing potential can be excluded wholesale from early clinical trials for the purpose of protecting the fetus, the presence of documented harm is not sufficient to exclude males with equal potential for childbearing. Rather, it is the degree of harm that determines whether a male will be included in a given clinical trial.

The practical result of the 1977 Guidelines was that drugs could be marketed without ever being tested on women. Ironically, the FDA could approve drugs, the toxicity of which was unknown in women and fetuses, for use on the very populations it sought to protect—pregnant women and women of childbearing potential.²⁴⁹ Moreover, by following FDA guidelines and attempting to "protect" women of childbearing potential (and

246. See 1 WOMEN AND HEALTH RESEARCH, *supra* note 3, at 137.

247. See 21 C.F.R. § 201.57(f)(b)(i)(c) (1995).

248. 1977 GUIDELINES, *supra* note 243, at 16.

249. See Merton, *supra* note 42, at 381-82 (observing that researchers bar almost all fertile women from research, but "when it comes time to prescribe, market, and profit from drugs, drug companies do not bar women, including women of childbearing capacity"). Merton notes that the researchers avoid responsibility for this apparent double standard by truthfully asserting that they have no information about the possible risks of the drug to pregnant women or fetuses. See *id.* at 382.

themselves from liability for research injuries), drug manufacturers could find themselves exposed to even greater potential liability should the adverse affects of a drug be discovered after it was marketed to the general public.²⁵⁰

The 1977 Guidelines were considered by many to reflect gender stereotyping more than concerns about good science.²⁵¹ In 1992, at the urging of women's health advocacy groups, the Congressional Caucus for Women's Issues requested a GAO audit of the FDA. As expected, the GAO found that women were underrepresented in drug trials, especially in the earliest stages of new drug research.²⁵² As a result of the GAO audit and public pressure, the FDA issued a new guideline in 1993 for the inclusion of women in drug research.

The FDA's 1993 Guideline, entitled "Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs,"²⁵³ loosened many of the restrictions it formerly had imposed on researchers and lifted the blanket ban on the inclusion of women of childbearing potential in new drug research.²⁵⁴ FDA policy now was beginning to move in the same direction of NIH policy on the inclusion of women.²⁵⁵

The 1993 Guideline provides that sponsors are expected to

250. Refer to Part IV *infra*.

251. See 1 WOMEN AND HEALTH RESEARCH, *supra* note 3, at 138 (citing Elvin L. Kinney et al., *Underrepresentation of Women in New Drug Trials*, 95 ANNALS INTERNAL MED. 495 (1981)).

252. See GENERAL ACCOUNTING OFFICE, *supra* note 203, at 2-3.

253. 58 Fed. Reg. 39,406 (1993).

254. See *id.* at 39,408. The FDA's intent in loosening its restrictions was to "remove the unnecessary Federal impediment to inclusion of women in the earliest stages of drug development." *Id.* In the background paper accompanying the 1993 Guideline, the FDA explained that the 1977 Guidelines may have "discouraged participation of women in drug development studies and may have resulted in a 'paucity of information about the effects of drugs in women.'" 1 WOMEN AND HEALTH RESEARCH, *supra* note 3, at 138-39 (citation omitted).

255. The FDA also acknowledged that its 1977 Guidelines were inconsistent with current policies prohibiting gender discrimination as interpreted by the United States Supreme Court in *UAW v. Johnson Controls, Inc.*, 499 U.S. 187 (1991). In *Johnson Controls*, the Court held that excluding all women, except those whose infertility was medically documented, from jobs involving actual or potential lead exposure exceeding OSHA guidelines was facially discriminatory and in violation of the Civil Rights Act of 1964. *Id.* at 211. The FDA maintained that removal of the prohibition on participation of women of child-bearing potential in Phase I and early Phase II trials is consistent with congressional efforts, laid out in the Pregnancy Discrimination Act and interpreted in *Johnson Controls*, to prevent unwarranted discrimination against such women. See 58 Fed. Reg. 39,408; Ruth Merkatz et al., *Women in Clinical Trials of New Drugs: A Change in Food and Drug Administration Policy*, 329 NEW ENG. J. MED. 292, 295 (1993) (maintaining that congressional action and Supreme Court decisions suggest that women should have the right to make their own risk-benefit choices about their pregnancies). For an in-depth discussion of the ethical and policy implications of *Johnson Controls*, refer to subpart IV(A).

include a full range of patients in their studies,²⁵⁶ to carry out appropriate analyses to evaluate potential subset differences in the patients they have studied,²⁵⁷ to study possible pharmacokinetic differences in patient subsets,²⁵⁸ and to carry out targeted studies to look for subset pharmacodynamic differences that are especially probable, suggested by existing data, or that would be particularly important if present.²⁵⁹ Consistent with its historical concern for fetal protection, the FDA also made clear that "[a]ppropriate precautions should be taken in clinical studies to guard against inadvertent exposure of fetuses to potentially toxic agents and to inform subjects and patients of potential risk and the need for precautions."²⁶⁰ What is new is the FDA's recognition that women, including those of childbearing potential, "are competent to give informed consent to their participation in research trials, and that this informed consent provides the necessary insulation to protect researcher and manufacturer from suit by mother or possible child for all but negligent enrollment practices."²⁶¹

Unfortunately, the 1993 Guideline has exceptions and other provisions that render it potentially weak. For example, the FDA undermines its own guidance that gender analyses be performed by stating that its recommendations need not always be followed.²⁶² In addition, the 1993 Guideline would not bar

256. "The patients included in clinical studies should, in general, reflect the population that will receive the drug when it is marketed. For most drugs, therefore, representatives of both genders should be included in clinical trials in numbers adequate to allow detection of clinically significant gender-related differences in drug response." 58 Fed. Reg. 39,410.

257. "Analyses to detect the influence of gender should be carried out both for individual studies and the overall integrated analyses of effectiveness and safety." *Id.* 258.

Using either a specific pharmacokinetic study or a pharmacokinetic screen, the pharmacokinetics of a drug should be defined for both genders. . . .

Three pharmacokinetic issues related specifically to women that should be considered during drug development are: (1) The influence of menstrual status on the drug's pharmacokinetics, including both comparisons of premenopausal and postmenopausal patients and examination of within-cycle changes; (2) the influence of concomitant supplementary estrogen treatment or systemic contraceptives (oral contraceptives, long-acting progesterone) on the drug's pharmacokinetics; and (3) the influence of the drug on the pharmacokinetics of oral contraceptives.

Id. at 39,410-11.

259. "Evidence of [pharmacodynamic] differences should be sought, however, in the data from clinical trials by carrying out the by-gender analyses suggested in the guideline on the clinical and statistical sections of NDA's." *Id.* at 39,411.

260. *Id.*

261. R. Alta Charo, *Protecting Us to Death: Women, Pregnancy, and Clinical Research Trials*, 38 ST. LOUIS L.J. 135, 158 (1993).

262. See 58 Fed. Reg. 39,408 (observing that "at this time [the FDA does not] perceive a regulatory basis for requiring routinely that women in general or women

a study protocol that required surgical sterilization for women of childbearing potential, nor does it prohibit sponsors from excluding women of childbearing potential without evidence of fetal toxicity.²⁶³ And, as under the 1977 Guidelines, Phase I testing in human subjects may begin prior to the completion of animal reproduction studies, thus restricting the right of both women and men to be fully informed of the potential reproductive risks of the therapy they are to receive.²⁶⁴

The FDA also failed to set forth its policy in regulation. The 1993 Guideline, therefore, does not have the force of law; it merely communicates recommended procedures to organizations who wish to market new drugs. Despite its recognition that the "change in FDA's policy will not, by itself, cause drug companies or IRB's to alter restrictions they might impose on the participation of women of childbearing potential,"²⁶⁵ the FDA nonetheless refrained from mandating the inclusion of women. The FDA rationalized that it was "confident that the interplay of ethical, social, medical, legal and political forces will allow greater participation of women in the early stages of clinical trials"²⁶⁶ and would not require inclusion of women in trials particularly routinely.²⁶⁷ The FDA's 1993 Guideline concluded with the following disclaimer: "This guideline does not bind the agency, and it does not create or confer any rights, privileges, or benefits for or on any person."²⁶⁸ Only time will tell whether or not the FDA is right.

of childbearing potential be included in particular trials").

263. See 59 Fed. Reg. 39,406.

264. The 1993 Guideline states that "[i]f no relevant information is available, the informed consent should explicitly note the potential for fetal risk." 58 Fed. Reg. 39,411. This provision may allow trial sponsors to place special conditions on the enrollment of women even when no analysis of reproductive effects has been undertaken. By allowing, if not encouraging, trial sponsors to do so, the FDA has substantially weakened the informed consent process and is, in effect, "in violation of its own duty to investigate the risk of adverse reproductive effects." THERESA MCGOVERN, PROPOSAL TO ELIMINATE OBSTACLES FACING WOMEN IN THE DRUG DEVELOPMENT PROCESS 21 (1994) (unpublished manuscript) (on file with the *Houston Law Review*). Further, because male-mediated reproductive effects need not be studied prior to human subjects testing, even though "special conditions" are not placed on their enrollment in clinical trials, men, too, are deprived of their right to be fully informed of potential reproductive risks. See *id.*

265. 58 Fed. Reg. 39,408.

266. *Id.* at 39,408-09.

267. *Id.* at 39,408.

268. *Id.* at 39,409.

IV. ETHICAL AND LEGAL IMPLICATIONS

Denying women access to clinical research and treatment raises questions of gender discrimination in the context of both statutory and constitutional law. Generally, the Supreme Court has affirmed women's rights to decisionmaking regarding behaviors that affect reproductive status.²⁶⁹ To date, however, there is little, if any, case law on the legal issues raised by clinical research and gender disparities in medical treatment. There is, however, a relatively recent Supreme Court case referred to and relied on by women's advocates and federal regulators alike to support the ethical, legal, and policy justifications for removing the barriers to women's participation in clinical research and recognizing the historical treatment of women for what it has been—gender discrimination.

A. Johnson Controls: *Laying the Ethical and Public Policy Foundation*

The Supreme Court, in *UAW v. Johnson Controls*,²⁷⁰ reasoned that decisions regarding future children are to be made by those who conceive and bear the children, not by employers or the courts.²⁷¹ *Johnson Controls* involved a fetal protection policy in which the company barred all fertile women from jobs involving lead exposure exceeding the standard set by the Occupational Safety and Health Administration for workers planning to have children.²⁷² Petitioners claimed that the policy violated Title VII as amended by the Pregnancy Discrimination Act (PDA).²⁷³

The Court found that the Johnson Controls policy created a facially discriminatory classification based on gender.²⁷⁴ In essence, the policy "[did] not pass the simple test of whether the evidence shows 'treatment of a person in a manner which but for that person's sex would be different.'"²⁷⁵ Because the pol-

269. See, e.g., *Roe v. Wade*, 410 U.S. 113, 154 (1973) (protecting a woman's right to obtain an abortion); *Griswold v. Connecticut*, 381 U.S. 479, 486 (1965) (protecting a married woman's right to contraceptive choice).

270. 499 U.S. 187 (1991).

271. See *id.* at 211. Refer to text accompanying note 315 *infra*.

272. *Johnson Controls*, 499 U.S. at 191-92.

273. See *id.* at 192. Refer to note 350 *infra* and accompanying text for the language of the PDA.

274. 499 U.S. at 197.

275. *Id.* at 200 (quoting *Los Angeles Dep't of Water & Power v. Manhart*, 435 U.S. 702, 711 (1978), quoting *Developments in the Law, Employment Discrimination and Title VII of the Civil Rights Act of 1964*, 84 HARV. L. REV. 1109, 1170 (1971)).

icy involved disparate treatment through explicit facial discrimination, the Court required Johnson Controls to establish that sex was a "bona fide occupational qualification [BFOQ] reasonably necessary to the normal operation of that particular business or enterprise."²⁷⁶

Although Johnson Controls alleged strong safety concerns, the Court pointed out the narrow circumstances under which the safety exception applied.²⁷⁷ Consequently, the company could not justify its policy on grounds that it was designed to protect pregnant women.²⁷⁸ Additionally, the Court favored the mother's dominion over her unborn or potential offspring rather than a fetal protection policy enforced by an employer.²⁷⁹ Turning toward legislative intent, the Court stated that "Congress made clear that the decision to become pregnant or to work while being either pregnant or capable of becoming pregnant was reserved for each individual woman to make for herself."²⁸⁰ Thus, Johnson Controls could not use fetal protection as a justification for its discriminatory policy.

The Court's holding in *Johnson Controls* relies on three conclusions. First, men rarely are excluded from activities based on concerns for their reproductive health. Whereas men are often given the choice of risking their reproductive futures, women are not granted these choices; therefore, this is in and of itself discrimination.²⁸¹ Second, the PDA prohibits discrimination based on pregnancy status. The Court noted that "'discrimination based on . . . pregnancy is, on its face, discrimination because of . . . sex.'"²⁸² Third, the lack of a "malevolent motive" and claims of beneficence do not overcome a presumption that a gender-based distinction is sex discrimination.²⁸³

The Court's reasoning sets the policy groundwork for addressing gender disparities in clinical research. While the *Johnson Controls* Court framed its discussion in the context of discrimination in the workplace, the decision nevertheless supports the policy position that excluding women from clinical trials by virtue of their reproductive health is discrimination against

276. *Id.* at 203 (citation omitted).

277. *See id.* at 202. The safety exception to the BFOQ defense generally applies where gender creates a risk to others and sex or pregnancy actually interferes with the employee's ability to perform the job. *See id.* at 204.

278. *See id.* at 206.

279. *See id.* at 206-07.

280. *Id.* at 206.

281. *See id.* at 197.

282. *Id.* at 199 (quoting *Newport News Shipbuilding & Dry Dock Co. v. EEOC*, 462 U.S. 669, 684 (1983)).

283. *See id.*

women as women. The Court also undercut rationales of nonmalevolence and beneficence as the basis for excluding women from the same opportunities as men.²⁸⁴ Although the early rationale for excluding women from clinical trials was based historically on ethical concerns designed to protect fetuses, those same concerns have served to restrict women's access to important clinical research on women's health and to potential treatment alternatives.

The *Johnson Controls* Court was not content to simply note that women should not be subjected to discrimination in general. It was very specific as to the latitude that women possess in making decisions about their own behaviors: women should not be forced to choose between pregnancy and a job,²⁸⁵ and the decision as to reproductive choice is to be left to the woman, not to the company.²⁸⁶ Thus, women are to be the sole arbiters of their decisions regarding their health behaviors.

Women should not be forced to choose between pregnancy and the availability of future treatment to participate in clinical trials. This is especially applicable to women with HIV when clinical trials may afford their only opportunity for access to treatment.²⁸⁷ The basis for this would be the Court's second provision, namely that decisions bearing on reproductive health status are to be exercised solely by a woman, not a company, and almost certainly not the government.²⁸⁸ The Court went on to note that approximately nine percent of all fertile women become pregnant per year and that this rate is much less in certain subgroups of women.²⁸⁹ The Court's strong message is that numbers of women "vulnerable" to pregnancy, whatever the number, are insufficient to discriminate against women as a whole.²⁹⁰ As to whether society may extend a paternalistic veto over a woman's decision, the Court further clarified its directive: "It is no more appropriate for the courts than it is for individual employers to decide whether a woman's reproductive role is more important to herself and her family than her economic role. Congress has left this choice to the woman as hers

284. See *id.*

285. See *id.* at 204 (emphasizing that women who are as capable as men to perform their jobs may not be forced to choose between having a child and having a job).

286. See *id.* at 206-07.

287. See Merton, *supra* note 42, at 377-78.

288. See *Johnson Controls*, 499 U.S. at 204, 211.

289. *Id.* at 207.

290. See *id.* ("[An employer's] fear of prenatal injury, no matter how sincere, does not begin to show that substantially all of its fertile women employees are incapable of doing their jobs.").

to make."²⁹¹

In spite of this strong language, it is important to emphasize again that *Johnson Controls* is a Title VII case involving sex discrimination in employment.²⁹² Thus, one might argue that *Johnson Controls* may not apply directly to the exclusion of women from clinical research and health care benefits. Yet, regardless of whether the legal holding of *Johnson Controls* extends beyond the employment context, the dictum provides the ethical and public policy foundation for addressing gender discrimination in clinical research and health care.

There is a real need for society to acknowledge that women are to be trusted in the decisions that they make for themselves and others. Women, as competent individuals, should be free to incorporate their own values and preferences into medical decisions that affect their bodily integrity. This would seem to place women, even those who are pregnant, in the best position to decide the advisability of entering a clinical trial. For women with AIDS, and for women with rare diseases, participation in a clinical trial represents a good in and of itself, in that access to the trial may literally be synonymous with the only available treatment.²⁹³ In addition, clinical trials provide good primary health care to women whose access to health care may be otherwise limited.²⁹⁴

B. Constitutional Issues

The exclusion of women from clinical research and other forms of health care raises important constitutional issues. The Fourteenth Amendment of the United States Constitution expressly prohibits states from taking any action that deprives any person of life or liberty or that denies any person the equal protection of the laws.²⁹⁵ Thus, some commentators and

291. *Id.* at 211.

292. *See id.* at 192.

293. *See* Merton, *supra* note 42, at 377-80 (arguing that clinical trials are treatments for many reasons: first, new and unlicensed drugs may be obtained only by serving as a research subject; second, patients are introduced to new applications of existing therapies; third, participants can receive therapies without charge; and finally, the program itself has many therapeutic aspects because of the attention and close monitoring the patient receives).

294. *See id.* at 379.

295. *See* U.S. CONST. amend. XIV, § 1. These provisions are "particularly relevant to questions of participation in clinical research." 1 WOMEN AND HEALTH RESEARCH, *supra* note 3, at 143; *see also* Megan R. Golden, Note, *When Pregnancy Discrimination is Gender Discrimination: The Constitutionality of Excluding Pregnant Women from Drug Treatment Programs*, 66 N.Y.U. L. REV. 1832, 1835 (1991) (arguing that refusal by drug treatment programs to treat pregnant women violates the

advocates have concluded that the "exclusion of women from government-sponsored or government-regulated research violates constitutional standards of liberty and equality."²⁹⁶

1. *Privacy and Liberty Interests.* Decisional privacy about matters affecting health care is among the liberties protected by the Fourteenth Amendment.²⁹⁷ Where fundamental rights are implicated, a policy that infringes upon them is subject to "strict scrutiny," and courts will strike down the policy unless the government can show that the policy furthers a "compelling" governmental purpose that cannot be achieved by a less restrictive means.²⁹⁸ The policy also must be narrowly tailored to meet its goal.²⁹⁹ To the extent that the exclusion of women of childbearing potential from clinical research and other forms of health care burdens a fundamental right, these policies are subject to the strict scrutiny test. If inclusion in clinical trials is not seen as a fundamental right, a lower standard of review would be applicable.

Much of the analysis regarding a woman's right to privacy and self-determination has evolved in the context of a woman's

Fourteenth Amendment).

296. 1 WOMEN AND HEALTH RESEARCH, *supra* note 3, at 143. Although private actors are not subject to constitutional governance, *see* *Shelley v. Kraemer*, 334 U.S. 1, 13 (1948) ("[A]ction inhibited by the first section of the Fourteenth Amendment is only such action as may fairly be said to be that of the States."), the argument can be made that private firms, such as pharmaceutical manufacturers, act in response to government regulation and have such close ties to the governmental agency that regulates them to classify their conduct as "government action" and subject to the principles of the Fourteenth Amendment. *See* *Jackson v. Metropolitan Edison Co.*, 419 U.S. 345, 350-51 (1974) (finding that a "heavily regulated utility with at least something of a governmentally protected monopoly" may possess sufficient nexus with the state to render the private utility a state actor); *see also* Dilan A. Esper, *Some Thoughts on the Puzzle of State Action*, 68 S. CAL. L. REV. 663, 683-85 (1995) (observing that, in certain contexts, the Supreme Court has found state action where government involvement appeared to be limited to regulation but has declined to do so in other contexts and hypothesizing that the Court predicates its nexus analysis to a large extent on the rights at issue rather than the level of government involvement in a particular case).

297. For example, the Court has recognized a competent individual's liberty interest with respect to the termination of artificial nutrition and hydration, *see* *Cruzan v. Director, Missouri Dep't of Health*, 497 U.S. 261, 279 (1990), reproductive rights with respect to contraceptive choice, *see* *Griswold v. Connecticut*, 381 U.S. 479, 486 (1965), and a woman's right to terminate a pregnancy, *see* *Roe v. Wade*, 410 U.S. 113, 154 (1973).

298. *See* LAURENCE H. TRIBE, *AMERICAN CONSTITUTIONAL LAW* § 16-7, at 1454 (2d ed. 1988).

299. *See* *United States v. Carolene Products Co.*, 304 U.S. 144, 152 n.4 (1938) ("There may be narrower scope for operation of the presumption of constitutionality when legislation appears on its face to be within a specific prohibition of the constitution").

right to abortion. In *Roe v. Wade*,³⁰⁰ the Supreme Court applied a strict scrutiny standard to strike down a state law that infringed upon a woman's fundamental right to terminate her pregnancy.³⁰¹ The issue as to whether the woman or the state retains a fundamental interest in medical decisionmaking has been further refined by the Court over the last two decades. In *Planned Parenthood v. Casey*,³⁰² the Supreme Court's most recent abortion ruling, the Court reaffirmed the core of *Roe* when it noted:

It must be stated at the outset and with clarity that *Roe*'s essential holding, the holding we reaffirm, has three parts. First is a recognition of the right of the woman to choose to have an abortion before viability and to obtain it without undue interference from the State. Before viability, the State's interests are not strong enough to support a prohibition of abortion or the imposition of a substantial obstacle to the woman's effective right to elect the procedure. Second is a confirmation of the State's power to restrict abortions after fetal viability, if the law contains exceptions for pregnancies which endanger a women's life or health. And third is the principle that the State has legitimate interests from the outset of the pregnancy in protecting the health of the woman and the life of the fetus that may become a child. These principles do not contradict one another; and we adhere to each.³⁰³

Casey has several implications for federal research regulations. The state has a legitimate interest in regulating clinical trials as a form of medical intervention, to protect the health of the woman and life of the fetus, much like it has the legitimate interest in regulating abortion as a medical procedure. However, while *Roe* established a woman's fundamental right to obtain an abortion, no fundamental right to health care in general, or to participate in clinical trials, in particular, has been established.³⁰⁴ Nevertheless, federal regulations that erect barriers to participation in clinical trials may infringe upon liberty interests, in effect placing concern for fetal well-being above the well-being of the mother. Such liberty interests can be found in two areas.

300. 410 U.S. 113 (1973).

301. See *id.* at 164-65.

302. 505 U.S. 833 (1992).

303. *Id.* at 846.

304. See Charo, *supra* note 261, at 152 (contending that a liberty interest should be implicated when women are denied potentially life-saving interventions, even though a constitutional right to health care does not exist).

The first group of liberty interests is grounded in personal autonomy and bodily integrity related to an individual's liberty interest in medical decisionmaking. The Court in *Casey* stated that "[j]ust as the Due Process Clause protects the deeply personal decision of the individual to *refuse* medical treatment, it also must protect the deeply personal decision to *obtain* medical treatment."³⁰⁵ Because participation in a clinical trial may be tantamount to obtaining the only life-saving or life-prolonging treatment currently available to a terminally ill person, the ability to choose this course of treatment is an issue of personal autonomy in medical decisionmaking.

The second group of protected interests are those related to "personal decisions relating to marriage, procreation, contraception, family relationships, child rearing, and education."³⁰⁶ These interests are implicated, for example, when a woman makes an informed choice to ingest a drug needed for health reasons that may or may not have teratogenic effects on future offspring.

Furthermore, the human subjects regulations requiring paternal consent for a pregnant woman to participate in a clinical trial significantly burden a woman's liberty interests and would not withstand constitutional challenge.³⁰⁷ Although the government has the right to regulate the conduct of clinical trials to protect all research subjects and ultimately the public at large, Subpart B creates a paternal veto that appears to contradict *Roe* and its progeny. In *Planned Parenthood v. Danforth*,³⁰⁸ the State attempted to argue that the decision to seek an abortion represented a change in family status and that both partners had interests in decisions affecting reproduction.³⁰⁹ The Court countered that the state could not grant

305. *Casey*, 505 U.S. at 927 n.3 (Blackmun, J., concurring in part, concurring in the judgment in part, dissenting in part) (relying on *Cruzan v. Director, Missouri Dep't of Health*, 497 U.S. 261 (1990)).

306. *Id.* at 851.

307. Requiring a reputed father's consent, pursuant to 45 C.F.R. §§ 46.207(b) & 46.208(b), is tantamount to veto power, not only over health matters involving a fetus, but, as a practical matter, over the mother seeking participation in a clinical trial (and accompanying treatment) for herself. Although the Supreme Court recognized in *Casey* that fathers do possess interests in their children that may be equivalent to a mother's interests, the Court distinguished children from fetuses and found that because decisions involving the latter affect the bodily integrity of the mothers carrying them, the liberty interests of pregnant women retain priority in these decisions. See *Casey*, 505 U.S. at 895-96. For a discussion of Subpart B and 45 C.F.R. §§ 46.207, 46.208, refer to notes 181-97 *supra* and accompanying text.

308. 428 U.S. 52 (1976).

309. See *id.* at 68.

power to an individual that the state itself did not have.³¹⁰ In other words, because the state cannot regulate abortion in the first trimester, that state lacks the constitutional power to grant to another—in this case, a reputed father—the power to veto a woman's decision to seek an abortion.³¹¹

The *Danforth* court rooted its decision in a basic privacy argument first enunciated in *Griswold v. Connecticut*,³¹² in which the Court held that a married individual's right to engage in reproductive decisionmaking and contraceptive use is protected.³¹³ The right to privacy was developed further in *Eisenstadt v. Baird*:³¹⁴ "If the right of privacy means anything, it is the right of the *individual*, married or single, to be free from unwarranted governmental intrusion into matters so fundamentally affecting a person as the decision whether to bear or beget a child."³¹⁵

Since *Roe v. Wade*, the Court has ruled consistently that decisions regarding reproduction remain exclusively with the woman in the first trimester. Furthermore, the Supreme Court has explicitly recognized that the woman as an *individual* adult has full decisionmaking power over both her reproductive status and decisions independent of any paternal interest. In *Danforth*, the Court determined that the individual whose choice should prevail is the woman's, as the one "who is the more directly and immediately affected by the pregnancy, as between the two."³¹⁶ Finally, the Court admitted that granting to a father virtual "veto power" over a mother's reproductive decisionmaking contravenes the state's intended goal of preserving the relationship between the two individuals.³¹⁷

This principle was reinforced in *Casey* when the Court affirmed the *Danforth* principle that there is no state aim to be met by giving one spouse veto power over the reproductive decisionmaking of another.³¹⁸ The weight of the decision should reside with the individual bearing the greatest burden of the decision, namely the woman herself.³¹⁹ The Court questioned

310. See *id.* at 69.

311. See *id.*

312. 381 U.S. 479 (1965).

313. See *Planned Parenthood v. Danforth*, 428 U.S. 52, 70 n.10 (1976) (citing *Griswold* and emphasizing the time honored notion of the right to privacy in marriage).

314. 405 U.S. 438 (1972).

315. *Id.* at 453.

316. *Danforth*, 428 U.S. at 71.

317. *Id.*

318. See *Casey*, 505 U.S. 833, 896 (1992).

319. See *id.* at 897.

whether a woman should be required to notify her partner and obtain his consent if she engages in behaviors regarding contraception or other activities such as surgery that may "potentially" affect her reproductive ability.³²⁰ In recognizing the dangers of allowing spousal notification, the Court further warned: "Perhaps next in line would be a statute requiring pregnant married women to notify their husbands before engaging in conduct causing risks to the fetus."³²¹

The Court, in commenting so directly on this issue, suggests how it might rule. Such a requirement would constitute an invasion of privacy and a violation of decisionmaking rights regarding behavior affecting reproduction, and, therefore, would be unconstitutional. The Court concluded that the Constitution "protects all individuals, male and female, married or unmarried, from the abuse of governmental power, even where that power is employed for the supposed benefit of a member of the individual's family."³²²

The *Casey* Court was not content to consider only the ramifications of spousal notification in principle, but engaged in rather extensive dicta describing spousal abuse that the Court speculated might result from the requirement of partner notification. The Court presented evidence that women of all social and economic levels are subject to abuse, citing statistics that pregnancy itself may incite a partner to violence that could be directed not only against the woman herself, but against other family members including children.³²³

Spousal notification also has repercussions for maintaining a woman's confidentiality regarding her pregnancy and preserving the overall well-being of the woman and her family. A requirement of spousal notification would mean that a woman's private reproductive decision could be revealed by a subpoena of her medical records; in addition, should a woman need to move her family to a shelter to protect them from an abusive partner, requiring spousal notification may reveal her location, resulting in further abuse to herself and her children.³²⁴

These latter points are especially relevant to pregnant women who wish to participate in clinical trials, particularly those women with HIV. As noted earlier, Subpart B requires

320. See *id.* at 898.

321. *Id.*

322. *Id.*

323. *Id.* at 892-93. Spousal abuse may not be limited to physical violence, but also may include psychological abuse and the restriction or elimination of economic resources to the family by the offending partner. *Id.* at 893.

324. See *id.* at 888-90.

that, absent certain exceptions, researchers may not only *notify*, but are required to obtain *consent* from the reputed father.³²⁵ Requiring a woman with HIV to notify her partner that she wishes to be included in a clinical trial for experimental HIV treatment for either her or the fetus (and to seek his consent) would be tantamount to a disclosure of her HIV status to that partner. The possibilities of physical or emotional abuse, or even separation from the partner, are realities for many women following disclosure of HIV status.³²⁶ The fear of domestic violence may preclude women with HIV, many of whom are poor with few economic opportunities or alternatives, from participating in a clinical trial that offers hope for their illness.³²⁷

Thus, requiring paternal consent invites exactly the type of potential abuse of the woman or her family described in *Casey*. Not only may the woman risk harm in an existing abusive situation by informing her partner that she is pregnant, but even more violence against the woman or her family may be induced by informing the partner of the woman's HIV status. Women are harmed in one of two ways by this requirement. Either they are excluded from a chance for treatment for themselves or they risk abandonment and violence from a partner who has been informed of the woman's HIV status.

2. *Equal Protection*. The Equal Protection Clause of the Fourteenth Amendment restricts the right of the government to treat similarly situated persons differently.³²⁸ Although there is

325. See 45 C.F.R. §§ 46.207(b), 46.208(b).

326. See Karen H. Rothenberg et al., *Domestic Violence and Partner Notification: Implications for Treatment and Counseling of Women with HIV*, 50 JAMWA 87, 91 (1995) (revealing that in a study of health care providers, fears of violence, abuse, and abandonment were among the most important for pregnant women with HIV in resisting spousal notification); Karen H. Rothenberg & Stephen J. Paskey, *The Risk of Domestic Violence and Women with HIV Infection: Implications for Partner Notification, Public Policy, and the Law*, 85 AM. J. PUB. HEALTH 1569, 1571 (1995) ("The data . . . suggest that some HIV-infected women may resist notification because they fear domestic violence, emotional abuse, or abandonment.").

327. In the ACTG 076 clinical trial, refer to note 193 *supra*, researchers reported that the requirement to obtain paternal consent did, in fact, prevent some women from participation. Women who otherwise might have been eligible for inclusion in the study were fearful that if paternal consent was sought they might risk domestic violence or abandonment following notification to the partner that she was HIV positive. Other women believed that the potential father had not expressed any interest in the pregnancy and had no right to decide whether she should participate in the clinical study. Telephone interviews with researchers at Johns Hopkins University and the University of Maryland, 1994-95; see also Edward M. Connor et al., *Reduction of Maternal-Infant Transmission of Human Immunodeficiency Virus Type 1 with Zidovudine Treatment*, 331 NEW ENG. J. MED. 1173, 1173 (1994) (describing the ACTG 076 trial and its results).

328. U.S. CONST. amend XIX. As with substantive due process analysis, state

no constitutional right to health care, it is a benefit whose distribution among similarly situated persons is constitutionally governed. The exclusion of women of childbearing potential from clinical research and other forms of health care is "*prima facie* disparate treatment of two classes of persons: [potentially] fertile females and all others."³²⁹ These exclusionary practices, then, are subject to constitutional scrutiny.

The Supreme Court has held that, for purposes of equal protection analysis, women occupy an intermediate status—historically disadvantaged, but not as disadvantaged as those "protected" classes that have been discriminated against because of race or illegitimacy. Policies and practices that have the purpose or effect of discriminating against women are thus subject to an intermediate level of scrutiny; to withstand constitutional challenge on equal protection grounds, "classifications by gender must serve important governmental objectives and be substantially related to the achievement of those objectives."³³⁰ As the Supreme Court later articulated, the government must have an "exceedingly persuasive justification" for its disparate treatment of men and women.³³¹

The "important government objective" is the protection of the mother and her fetus from injury.³³² In the case of the FDA, exclusionary policies also are meant to promote consumer protection through the safety and efficacy of drugs approved for marketing.³³³ The question, then, is whether the exclusion of all women, or a particular subset of women, from clinical research and certain other forms of health care is substantially related to

action is required. See *Shelley v. Kraemer*, 334 U.S. 1, 13 (1948) ("[A]ction inhibited by . . . the Fourteenth Amendment is only such action as may fairly be said to be that of the states."). The NIH and FDA are state actors governed by the Constitution, and their policies and regulations are subject to equal protection review. See Merton, *supra* note 42, at 423-24 (maintaining that research supported by the NIH should adhere to constitutional standards). In addition, the conduct of a private research or health care organization may be considered state action by virtue of any close regulation by and funding from federal, state, and local government. See, e.g., Golden, *supra* note 295, at 1866.

329. Charo, *supra* note 261, at 149.

330. *Craig v. Boren*, 429 U.S. 190, 197 (1976).

331. *Mississippi Univ. for Women v. Hogan*, 458 U.S. 718, 724 (1982) (citations omitted).

332. See 1 WOMEN AND HEALTH RESEARCH, *supra* note 3, at 148 (predicting that the government would argue that protecting potential life is an important government objective).

333. See Ronald Podraza, *The FDA's Response to AIDS: Paradigm Shift in New Drug Policy?*, 48 FOOD & DRUG L.J. 351, 356-57 (1993) ("The new drug approval statutes and regulations have a dual purpose: (1) consumer protection, and (2) enforcement of recognized scientific criteria in the conduct of studies performed for the purpose of proving a drug's safety and effectiveness.").

the government objectives of protection for women and their fetuses and the marketing of safe, efficient drugs.

In the context of research, the FDA's 1977 Guidelines that authorized the exclusion of women from early, if not all, phases of drug trials could not meet the "substantially related" prong of the test for constitutionality.³³⁴ Moreover, by authorizing the exclusion of all women of childbearing potential from clinical trials, the FDA, in effect, approved drugs for marketing to women without any testing at all of the potential danger to women or their fetuses. This is clearly in direct contradiction with and not substantially related to the government's intention to protect these populations.³³⁵ Fetal protection regulations that overlook the role of male factors in causing fetal defects also do not guarantee overall fetal well-being; there is evidence now that birth defects may be transmitted via damaged sperm.³³⁶ In fact, the "overinclusiveness" of Subpart B is also subject to equal protection challenges because it singles out pregnant women for exclusion from clinical research.³³⁷

It has been argued, however, that discrimination based on reproductive status is not gender discrimination per se. Rather, the two classes of individuals distinguished for unequal treatment are women who are capable of becoming pregnant and persons who are not capable of becoming pregnant, a class that would include some women as well as all men.³³⁸ This reasoning is subject to question. A policy that distinguishes between these groups is, on its face, gender neutral. To be upheld, such a policy need only be rationally related to a legitimate government interest unless it is found to be intentionally discriminatory. In

334. See 1 WOMEN AND HEALTH RESEARCH, *supra* note 3, at 147 (arguing that the exclusion of women of childbearing potential would violate the Equal Protection Clause). Other discriminatory practices, such as the exclusion of all pregnant women from substance abuse treatment programs, would require individualized determinations of the sufficiency of the government actor's rationale for the practice. See Golden, *supra* note 295, at 1869 ("The drug treatment programs' policies [that exclude pregnant women] thus should be treated as a gender classification, subject to heightened judicial scrutiny. As such, they should be held to violate the equal protection clause unless they are substantially related to an important government interest.").

335. See 1 WOMEN AND HEALTH RESEARCH, *supra* note 3, at 147. A great number of drugs that are prescribed to women are tested only on women in the marketplace when prescribed. See Merton, *supra* note 42, at 380-81 (describing women as "guinea pigs" when a new treatment hits the market). For drugs that are prescribed to pregnant women, the lack of dosage studies prevents establishing minimal dosing levels that would serve to limit harm to both women and fetuses. See *id.* at 385-86.

336. See Merton, *supra* note 42, at 392 n.107, 396 (discussing the failure of policies to address male-mediated reproductive outcomes).

337. See 1 WOMEN AND HEALTH RESEARCH, *supra* note 3, at 147.

338. See *id.* at 148 (analyzing *Geduldig v. Aiello*, 417 U.S. 484 (1974)).

Geduldig v. Aiello,³³⁹ the Supreme Court upheld a state's decision to exclude disabilities resulting from pregnancy from coverage under the state's disability insurance program.³⁴⁰ Reasoning that all classifications involving pregnancy do not necessarily amount to classification based on gender for the purpose of equal protection analysis,³⁴¹ the Court applied the rational basis standard of review and concluded that the state's disability coverage policy was rationally related to several legitimate interests.³⁴²

Geduldig can be distinguished from the proposition that excluding women of childbearing potential from clinical research is not gender discrimination. The underlying basis of the *Geduldig* holding was the fact that the benefits that were available under the disability insurance program were available equally to men and women.³⁴³ Pregnant women received the same coverage as nonpregnant persons.³⁴⁴ In the context of clinical research, women of childbearing potential are *not* provided the same benefits, including the opportunity to participate in clinical trials and receive the provided therapies, as persons who are not capable of becoming pregnant.

Equal protection may also apply to "benign classifications," which favor one group over another, in order to remedy past discrimination.³⁴⁵ Arguably, then, the NIH Revitalization Act, which requires the affirmative inclusion of women in clinical studies, would constitute a benign classification.³⁴⁶ If a man challenged the constitutionality of this statute on grounds of disparate treatment, the intermediate scrutiny test for application to exclusion also would be applicable.³⁴⁷ The success of such a challenge might depend on whether the government could present

339. 417 U.S. 484 (1974).

340. *See id.* at 497.

341. *See id.* at 496 n.20 ("While it is true that only women can become pregnant it does not follow that every legislative classification concerning pregnancy is a sex-based classification . . .").

342. *See id.* at 496. The Court recognized the state's interest in maintaining the self-supporting nature of its insurance program (it would have been very costly to include pregnancy-related disability in its insurance scheme), distributing available resources so as to keep benefit payments at adequate levels for those disabilities that were covered, and maintaining a contribution rate not unduly burdensome to participating employees. *See id.* at 495-96. For a creative analysis of *Geduldig*, see Golden *supra* note 292, at 1856-66 (arguing that *Geduldig* is consistent with intermediate scrutiny).

343. *See Geduldig*, 417 U.S. at 496-97.

344. *Id.*

345. 1 WOMEN AND HEALTH RESEARCH, *supra* note 3, at 149-50.

346. *See id.* at 150.

347. *See id.* at 147.

evidence of past discrimination against women in clinical research to justify the disparate treatment.³⁴⁸

C. Federal and State Antidiscrimination Statutes

Statutory protection against gender discrimination in employment is set out in Title VII of the Civil Rights Act.³⁴⁹ The Pregnancy Discrimination Act (PDA), which was made part of Title VII, protects employed women who are pregnant.³⁵⁰ Title VII protects against disparate treatment of men and women and against practices that create disparate impacts on different classifications of people.³⁵¹

As noted earlier, the Supreme Court, in *Johnson Controls*, held that a fetal protection policy that prevented fertile women from certain employment opportunities violated Title VII and the PDA.³⁵² First, the Court found the policy was gender-specific because it applied only to the potential offspring of the female employees "[d]espite evidence in the record about the debilitating effect of lead exposure on the male reproductive system."³⁵³ This practice of the differential application of privileges to men and women constituted gender discrimination.³⁵⁴ The Court also reasoned that despite potential risks to offspring, Title VII provided that "[w]omen who are pregnant or potentially pregnant must be

348. See *id.* at 150.

349. 42 U.S.C. § 2000e-2 (1988).

350. Although Title VII explicitly prohibits sex discrimination, it did not originally mention pregnancy discrimination, allowing the Supreme Court in *General Electric Co. v. Gilbert*, 429 U.S. 125 (1976) to hold that certain pregnancy classifications did not constitute gender discrimination. See *id.* at 139-40. In response, Congress passed the PDA "to change the definition of sex discrimination in Title VII to reflect the commonsense view" that pregnancy discrimination is gender discrimination. HOUSE COMM. ON EDUC. & LABOR, PROHIBITION OF SEX DISCRIMINATION BASED ON PREGNANCY, H.R. REP. NO. 95-948, 95th Cong., 2d Sess. 3 (1978). The PDA provides, in relevant part:

The terms "because of sex" or "on the basis of sex" include, but are not limited to, because of or on the basis of pregnancy, childbirth, or related medical conditions; and women affected by pregnancy, childbirth, or related medical conditions shall be treated the same for all employment-related purposes . . . as other persons not so affected but similar in their ability or inability to work . . .

42 U.S.C. § 2000e(k) (1988).

351. See *Gilbert*, 429 U.S. at 136-37 (describing that "a prima facie violation of Title VII can be established in some circumstances upon proof that the effect of an otherwise facially neutral plan or classification is to discriminate against members of one class or another").

352. See *UAW v. Johnson Controls*, 499 U.S. 187, 211 (1991). Refer to subpart IV(A) *supra*.

353. *Johnson Controls*, 499 U.S. at 198.

354. See *id.* at 197.

treated like others."³⁵⁵

Because Title VII only applies in the employment context, its legal application to clinical research and other health care may be limited.³⁵⁶ At least when a study uses paid participants, the subjects' participation may be considered "employment," and exclusionary practices in this context may be subject to Title VII scrutiny.³⁵⁷ In any case, the ethical and policy foundation established by *Johnson Controls* is quite significant.³⁵⁸

Gender discrimination in research also may be prohibited by Title IX, which states that "[n]o person in the United States shall, on the basis of sex, be excluded from participation in, be denied the benefits of, or be subjected to discrimination under any education program or activity receiving Federal financial assistance."³⁵⁹ One commentator has argued that Title IX might provide the basis for a sex discrimination claim by women excluded from clinical research conducted at educational institutions receiving federal funds.³⁶⁰

Recently, claims under federal antidiscrimination statutes, including Title VII, are being raised in courts by women seeking access to high-dose chemotherapy (HDCT) and autologous bone marrow transplant (ABMT) for breast cancer.³⁶¹ It is alleged that employers and group health insurers with whom they contract discriminate by paying for HDCT/ABMT for some cancers, but not for breast cancer.³⁶² On June 16, 1995, the Eighth Circuit Court of Appeals ruled that an employer and its

355. *Id.* at 204.

356. See, e.g., Mary A. Bobinski, *Women and HIV: A Gender-Based Analysis of a Disease and Its Legal Regulation*, 3 TEX. J. WOMEN & L. 7, 21-22 (1994) (considering a claim in the context of women with HIV attempting to obtain access to research trials). Refer to subpart IV(A) *supra* for a discussion of *Johnson Controls*, a Title VII case.

357. See Merton, *supra* note 42, at 423 (suggesting that in "the rare circumstance" where the subjects are paid, the participation could be considered a form of employment).

358. Refer to subpart IV(A) *supra*.

359. 20 U.S.C. § 1681(a) (1994).

360. See Bobinski, *supra* note 356, at 22 n.55. "Potential research participants excluded by reason of their gender might be entitled to relief under this provision, but would have to establish that they are 'persons' protected from discrimination under the Act and that their exclusion from research trials constituted 'discrimination.'" *Id.*

361. See *Henderson v. Bodine Aluminum, Inc.*, 70 F.3d 958, 959 (8th Cir. 1995) (raising claim under the Americans with Disabilities Act for denial of health coverage for HDCT); *Reger v. Espy*, 836 F. Supp. 869, 870 (N.D. Ga. 1993) (charging that denial of coverage for HDCT/ABMT for breast cancer violates the Federal Employees Health Benefits Act). In addition, these claims charge violations of the Americans with Disabilities Act, 42 U.S.C. §§ 12101-12213 (Supp. V 1993), and of various state antidiscrimination laws that might prohibit sex discrimination or discrimination based on disability. See *Henderson*, 70 F.3d at 959.

362. *Henderson*, 70 F.3d at 959; *Reger*, 836 F. Supp. at 871-72.

health insurer could be required to pay for such treatments, even though such coverage was excluded specifically under the terms of the insurance policy.³⁶³ Without payment assurance, the plaintiff was not able to enroll in a clinical trial that might have afforded her the best chance of survival.³⁶⁴ Although this case, and others like it, involve payment issues, they directly impact women's access to research and treatment.³⁶⁵

Gender discrimination is not addressed in other federal laws barring discrimination by recipients of federal funds, in public facilities, or by places of public accommodation.³⁶⁶ However, gender discrimination is regulated by state statutes prohibiting discrimination in places of "public accommodation."³⁶⁷ Public accommodations might include facilities such as clinics, hospitals, private doctors, and dentists. These laws potentially provide a cause of action for women seeking access to clinical research and treatment, with at least one court showing a willingness to examine state antidiscrimination laws within the context of women's health care services.

In *Elaine W. v. Joint Diseases Northern General Hospital, Inc.*,³⁶⁸ pregnant women as a class were denied enrollment in a hospital substance abuse program.³⁶⁹ The hospital defended its policy based on the medical grounds that it lacked the services of an obstetrician, and it was therefore not licensed to

363. See *Henderson*, 70 F.3d at 962. Currently, at least six states either have passed or are considering legislation mandating that insurers offer coverage for HDCT/ABMT treatment of delineated cancers, including breast cancer. See GA. CODE ANN. § 33-29-3.3 (Supp. 1995) (ABMT); MASS. GEN. LAWS ANN. ch. 175, § 47M (West Supp. 1995) (ABMT); MO. ANN. STAT. §§ 376.782, 376.1200 (Vernon Supp. 1996); N.H. REV. STAT. ANN. § 415:18-c (Supp. 1994) (ABMT); VA. CODE ANN. § 38.2-3418.1:1 (Michie 1994) (HDCT and ABMT); Health Insurance—Breast Cancer Treatment, H.F. No. 1742, 1995 Minn. Sess. Law Serv. (to be codified at MINN. STAT. § 62A.307). Pursuant to the United States Office of Personnel Management and Policy (OPM), all health insurance plans provided to federal employees must offer such treatment for breast cancer, as well as a number of other cancers, as a mandated benefit. Telephone interview with OPM staff, July 1995.

364. See *Henderson*, 70 F.3d at 960.

365. It is unclear to what extent the provision of employee health benefits in this context would fall within the reach of Title VII. Furthermore, short of explicitly excluding procedures for all women, it might be difficult to demonstrate disparate impact.

366. See Bobinski, *supra* note 356, at 22 n.55.

367. See, e.g., N.Y. EXEC. LAW § 296(2)(a) (McKinney 1993) ("It shall be an unlawful discriminatory practice for any . . . owner . . . or employee of any place of public accommodation, . . . to [refuse, withhold from, or deny] any of the accommodations, advantages, facilities and privileges of any such place . . . to any person on account of . . . sex . . .").

368. 613 N.E.2d 523 (N.Y. 1993).

369. See *id.* at 524.

provide obstetrical care to the women.³⁷⁰ The New York Court of Appeals ruled that the hospital's use of a medical explanation to exclude a class did not justify discrimination if the discriminatory behavior was based in fact on generalities surrounding the medical condition.³⁷¹ The court declared that any wholesale exclusion of pregnant women must be medically warranted.³⁷² The facility had the burden to show that absolutely no pregnant woman could be treated regardless of her health, stage of pregnancy, or the severity of her addiction.³⁷³ Alternatively, the facility would have to demonstrate that it could not identify "with reasonable medical certainty" those women who would require "immediate on-site obstetrical services" during their treatment for substance abuse.³⁷⁴

The New York court observed that "[m]any discriminatory practices develop improperly because of a paternalistic sense of what is 'best' for those who are discriminated against."³⁷⁵ The burden lies with medical facilities to show a medical basis for the discriminatory practice.³⁷⁶ A demonstration that some, or even most, of the recipients should be denied access on medical grounds is insufficient to deny the entire class of pregnant women.³⁷⁷ Therefore, distinctions based solely on a pregnant condition constitute sex discrimination.³⁷⁸ Consequently, state antidiscrimination laws may potentially provide a basis for protecting women's access to research and treatment in places of public accommodation.³⁷⁹

370. *See id.*

371. *See id.* at 524-25 (holding that distinctions based solely upon a woman's pregnant condition constitutes sexual discrimination).

372. *See id.* at 524.

373. *See id.* at 525.

374. *Id.* at 525, 526.

375. *Id.* at 525-26.

376. *See id.* at 525.

377. *See id.* at 526.

378. *See id.* (stating that "[e]ven a true generalization about the class is an insufficient reason for disqualifying an individual to whom the generalization does not apply" (quoting *Los Angeles Dep't of Water & Power v. Manhart* 435 U.S. 702, 708 (1978) (alteration in original))).

379. One commentator suggests a contrary view:

[The *Elaine W.*] holding, while technically favorable for plaintiffs seeking to challenge the exclusion of women from drug treatment centers, is nevertheless quite limited. It provides no support for the argument that hospitals which purport to provide drug treatment programs should make available the full range of medical services that might be needed by program participants, including obstetrical services.

Bobinski, *supra* note 356, at 23.

D. Tort Liability

Medical researchers and pharmaceutical manufacturers share a fear that if a woman participating in research becomes pregnant and her fetus is harmed, they will be held liable.³⁸⁰ This fear is often the reason for the exclusion of women from clinical trials, despite a very low reported incidence of research injuries³⁸¹ and few reported legal cases concerning such injuries.³⁸² Fear of liability, however, has not operated to exclude men from participating in clinical trials, despite evidence that some fetal injury may be attributed to the father's exposure to toxic substances.³⁸³ Ironically, fear of liability has never operated as a rationale for the inclusion of women in clinical research, even though there may be more legal precedent for liability due to exclusion.³⁸⁴

1. Liability for Inclusion.

[I]t is impossible to quantify the risk of tort liability from the inclusion of women in clinical studies at this time, because: (1) there is no complete compendium of *unreported* cases involving settlements and (2) pregnant women and women of childbearing age have not been included in some major studies in the past.³⁸⁵

Potential liability for injuries to women (and men) who participate in clinical research is unlikely, provided that informed

380. See 1 WOMEN AND HEALTH RESEARCH, *supra* note 3, at 150.

381. See *id.* at 151. NIH and the FDA do not require researchers or sponsors to report research injuries. While no central registry of publicly or privately funded research injuries exists, a 1975 survey of principal investigators indicates the incidence of injury to be about 3.7%. *Id.* Less than 1% of research participants suffered permanently disabling or fatal injuries. *Id.* The incidence of injury in this survey was not separated by gender or age. *Id.*

382. See *id.* NIH has been involved in three legal actions in the last 20 years. See *id.* One case brought against NIH directly was dismissed, and the other two were tried against NIH grantee institutions. See *id.* at 170 n.5. Furthermore, the FDA has never been sued for a clinical trial injury, and private firms have been involved only in approximately two dozen reported cases. See *id.* at 151.

It is possible that legal recourse for research injuries is not sought in many cases because of the fact that prior to enrollment in a clinical trial, the potential participant is given a detailed description of the risks and benefits of the proposed therapy, as well as their likelihood. See *id.* at 152. While enrolled in the trial, participants receive not only the test therapy, but also a fairly high level of medical care. See *id.* Participants may therefore feel that they have assumed the risks of participating in the clinical trial and have no right to pursue a claim for injuries. See *id.*

383. See *id.* at 150.

384. See *id.*

385. *Id.* at 12-13.

consent to participate in the research is obtained in accordance with federal regulations and state tort law.³⁸⁶ Federal regulations on disclosure may help to establish the standard of care in a particular situation.³⁸⁷ Even if a woman who has been injured as a result of her participation in a clinical trial could prove the necessary elements for recovery under a negligence theory, researchers and manufacturers nonetheless may have defended themselves from liability for her injuries by securing her informed consent prior to participation in the trial.³⁸⁸

Liability, then, turns on the "informed" nature of the woman's consent to participate in the research—whether she has been adequately warned of the potential risks of the research.³⁸⁹ If the researcher has met the requisite standard of care by warning the woman of the potential risks of the trial in which she wishes to participate, and if she chooses to participate, it is unlikely that she will succeed in any subsequent negligence action for injuries that may occur as a result of her participation in the trial.

Under strict liability principles, however, a defendant will be held liable for injuries resulting from his or her unreasonably dangerous activity.³⁹⁰ In the context of clinical research, liability may be found regardless of the woman's informed consent to participate.³⁹¹ Providing adequate warning of the risks of the

386. See 45 C.F.R. §§ 46.116-.117 (delineating general requirements and documents for informed consent). In the context of research, a battery action may be brought if the participant is subjected to a study without her knowledge or consent. See 1 WOMEN AND HEALTH RESEARCH, *supra* note 3, at 153. If the initial consent to participate did not include adequate disclosure of risks and alternatives, the legal action will be based on negligence for lack of informed consent. See *id.* at 13, 153-54.

387. See 1 WOMEN AND HEALTH RESEARCH at 154, 156. In some states, the standard of reasonable disclosure is defined as the customary practice of physicians; other states use the prudent person standard where inquiry is made into what a prudent person in these circumstances would want to know. See *id.* at 156.

388. See *id.* at 152, 155.

389. Federal regulations, as well as FDA guidelines, require researchers and IRBs to obtain the informed consent of all persons who participate in clinical research. See *id.* at 158-59. The standard for what constitutes informed consent varies from state to state, but in general, three standards exist in the context of medical malpractice. Some states allow a physician to disclose a level of information regarding risks and benefits that is customary for physicians practicing in the community. See *id.* at 156. Some states require physicians to disclose all information that a "prudent person" in the patient's position would want to know. See *id.* In a few other states, a more subjective standard has been adopted, requiring physicians to disclose all information needed to allow the particular patient to make an informed decision. See *id.* at 156-57. Recently, a federal court held that a higher standard for informed consent—a duty to inform a potential participant of all "reasonably foreseeable" risks—is required for participation in nontherapeutic research injury cases. See *Whitlock v. Duke Univ.*, 637 F. Supp. 1463, 1472 (M.D.N.C. 1986), *aff'd*, 829 F.2d 1340 (4th Cir. 1987).

390. See 1 WOMEN AND HEALTH RESEARCH, *supra* note 3, at 154.

391. See *id.*

experimental therapy or drug, however, may insulate the researcher or manufacturer from liability.³⁹² Moreover, it is possible that strict liability principles do not apply to drug trials.³⁹³ Case law suggests that manufacturers of experimental drugs, as well as providers of experimental medical services, may not be held strictly liable for the effects of the drugs or services if the participants in the clinical research have given legally sufficient informed consent to participate and the trial is conducted appropriately.³⁹⁴

Questions of liability more often focus on potential harm to the future offspring of women who participate in clinical trials.³⁹⁵ It is unclear in this context whether obtaining the informed consent of the mother would be sufficient to avoid liability for the injury to the offspring. To date, there has been virtually no case law establishing parameters for holding researchers or drug manufacturers liable for injuries to the offspring of clinical trial participants;³⁹⁶ however, liability can be analyzed by looking to the purpose of the clinical trial in which the mother participated.

392. See *id.*

393. See *id.* at 154-55 (noting that strict liability applies when a product is sold in a defective, unreasonably unsafe condition). In a clinical trial, however, the manufacturer is not selling the drug to a participant. *Id.* Therefore, a participant who is injured by an experimental drug may have no recourse against a manufacturer for her injury based on the theory of strict liability. See *id.* (citing Ellen Flannery & Sanford N. Greenberg, *Liability Exposure for Exclusion and Inclusion of Women as Subjects in Clinical Studies*, in 2 WOMEN AND HEALTH RESEARCH, *supra* note 3). This argument is supported by comment k to § 402A of the *Restatement (Second) of Torts*, which protects a drug manufacturer from strict liability if a drug is "properly prepared and marketed, and proper warning is given." *Restatement (Second) of Torts*, § 402A, comment k (1964). Comment k also applies this protection to experimental drugs, in particular, where, "because of lack of time and opportunity for sufficient medical experience, there can be no assurance of safety." *Id.*

394. See, e.g., *Gaston v. Hunter*, 588 P.2d 326, 340-41 (Ariz. Ct. App. 1978) (holding that an experimental drug manufacturer was not strictly liable when the warning was adequate, possible risks were outweighed by possible benefits to society, and the plaintiff voluntarily participated in the dangerous activity). It is interesting to note, however, that the *Gaston* court first rejected the notion that strict liability would not apply to drugs in the experimental phase because they were not sold. See *id.* at 339; see also *Doe v. Miles Labs., Inc.*, 927 F.2d 187, 193 (4th Cir. 1991) (applying the medical services exemption to producers of blood products).

395. See 1 WOMEN AND HEALTH RESEARCH, *supra* note 3, at 159. "The child, if he is born alive, is now permitted in every jurisdiction to maintain an action for the consequences of prenatal injuries, and if he dies of such injuries after birth an action will lie for his wrongful death." W. PAGE KEETON ET AL., *PROSSER AND KEETON ON THE LAW OF TORTS* § 55, at 368 (5th ed. 1984) (footnotes omitted).

396. There have been only two cases of reported research injuries to offspring. See 1 WOMEN AND HEALTH RESEARCH, *supra* note 3, at 162. In both cases, the University of Chicago was found liable because it had failed to obtain consent to experiment with DES on pregnant women. See *id.* at 162 (analyzing *Roberts v. Patel*, 620 F. Supp. 323 (N.D. Ill. 1985) and *Mink v. University of Chicago*, 460 F. Supp. 713 (N.D. Ill. 1978)).

The first, and fairly clear-cut, case would involve participation in a clinical trial where the treatment received was therapeutic for the fetus. In such a case, it is unlikely that liability would be found when informed consent to the treatment was provided to further the best interest of the fetus and improve its health.³⁹⁷

Some commentators have reasoned that the result would be less clear if participation in the clinical trial was sought because the experimental treatment or drug was designed to be therapeutic for the mother only.³⁹⁸ In such a case, liability might rest on an analysis of the seriousness of the mother's illness, the risks to the fetus, and the existence of any safer alternatives.³⁹⁹ When balancing these factors, however, the woman's health and autonomy interests should not be subordinated to those of the fetus.⁴⁰⁰

Thus, it appears that when there is no negligence and the appropriate informed consent to participation in a clinical trial has been obtained, it is unlikely, but not impossible, that researchers and sponsors will be held liable in tort for the inclusion of women in their studies.⁴⁰¹ Furthermore, the possibility of tort liability seems "remote at best" when viewed in the context of the Supreme Court's rejection in *Johnson Controls* of the employer's fear of liability as a justification for its discriminatory fetal protection policy. In so holding, the Court reasoned that

397. See *id.* (citing *Roberts* and holding that a parent may consent for treatment on the unborn fetus).

398. See, e.g., *id.* at 162-63.

399. See *id.* If the intervention is a benefit to the mother (but not for a serious illness), or if there is a known risk to the fetus and there are safer treatment alternatives, the risk of liability may be higher for the drug manufacturer or trial sponsor. See *id.* at 163. There is also the rare possibility that a woman may wish to participate in clinical research where the experimental treatment is not therapeutic for her or her fetus. See *id.* Subpart B would virtually exclude most of this type of research. See *id.*

400. See *id.* at 17 ("[P]regnant women should be treated as competent adults capable of making their own decisions about participation in research."); see also *In re A.C.*, 573 A.2d 1235, 1252 (D.C. 1990) (holding that in virtually all cases the question of what is to be done is to be decided by the patient on behalf of herself and the fetus).

401. See 1 WOMEN AND HEALTH RESEARCH, *supra* note 3, at 163-64. At least one commentator has argued that there may be "settings in which third parties are not entitled to rely on even the fully informed consent of prospective parents to immunize them from later liability if the protocol poses very serious risks to the unborn child while offering little benefit to the subject adult or to adults in general." See Ellen W. Clayton, *Liability Exposure When Offspring Are Injured Because of Their Parents' Participation in Clinical Trials*, in 2 WOMEN AND HEALTH RESEARCH, *supra* note 3, at 103, 107. On the other hand, one could argue that because informed consent obtained from the woman acts as an intervening cause in the injury to the offspring, there is no legal precedent for holding a researcher liable. See Merton, *supra* note 42, at 407.

"[i]f, under general tort principles, Title VII bans sex-specific fetal-protection policies, the employer fully informs the woman of the risk, and the employer has not acted negligently, the basis for holding an employer liable seems remote at best."⁴⁰²

In his concurring opinion, Justice White observed that "it is far from clear that compliance with Title VII will pre-empt state tort liability."⁴⁰³ In response, the majority reasoned that the law would not punish an employer who complied with Title VII because "[w]hen it is impossible for an employer to comply with both state and federal requirements, this Court has ruled that federal law pre-empts that of the States."⁴⁰⁴ It also maintained that the increased cost of employing women of childbearing potential, including the cost of liability insurance, could not justify an exclusionary policy that discriminates on the basis of gender.⁴⁰⁵ Based on this reasoning, *Johnson Controls* lends support to the argument that the federal policy encouraging, if not mandating, the inclusion of women in clinical research should not be undermined based on the fear of tort liability by researchers, drug manufacturers, and other third parties. Furthermore, even though *Johnson Controls* is an employment discrimination case, it reinforces the importance of adequate informed consent as a means of promoting the autonomy of women, as well as men, and of reducing any likelihood of tort liability for the inclusion of women in clinical research.

2. *Liability for Exclusion.* Liability for the exclusion of women from clinical research may occur when a woman takes a drug or receives a treatment that was untested in women during the clinical trials. The evolution of public policy that establishes the importance of including women in clinical research has prompted commentators to suggest that researchers and drug manufacturers should focus their concern on liability that results from the exclusion of women from clinical research.⁴⁰⁶ Unlike speculation about liability for inclusion, legal precedent that has based liability, in part, on the inadequate testing of a drug before it was released into the market does exist.⁴⁰⁷ It is also possible

402. *UAW v. Johnson Controls*, 499 U.S. 197, 208 (1991).

403. *Id.* at 213 (White, J., concurring).

404. *Id.* at 209 (citing *Florida Lime & Avocado Growers, Inc. v. Paul*, 373 U.S. 132, 142-43 (1963)).

405. *See id.* at 210.

406. *See* 1 WOMEN AND HEALTH RESEARCH, *supra* note 3, at 13 (proposing that liability concerns should not impede inclusion of women in clinical studies).

407. *See, e.g., Tinnerholm v. Parke, Davis & Co.*, 285 F. Supp. 432 (S.D.N.Y. 1968), *modified on other grounds*, 411 F.2d 48 (2d Cir. 1969); *West v. Johnson & Johnson Prods., Inc.*, 220 Cal. Rptr. 437 (Ct. App. 1985), *cert. denied*, 479 U.S. 824 (1986);

that a medical malpractice claim could result from the inappropriate application of a treatment regimen that was developed through research in which only men were studied. Thus, in contrast to liability for a research injury that results from being included in research, liability for exclusion may result from the lack of data necessary to establish appropriate standards for the treatment of women.

Drug manufacturer liability may be found where physiological differences exist between men's and women's responses to a particular drug, causation between the drug and the woman's injury can be established, and the manufacturer fails to test the drug on women.⁴⁰⁸ If a woman who takes the drug has an adverse reaction or if her future offspring is harmed, it would be her exclusion from research, not her inclusion, that caused the injury and that forms the basis for liability. Applying strict liability principles, a defectively designed product may serve as the basis for liability should an injury occur. A drug that has not been adequately tested on women may be found to be defectively designed, even if approved for marketing by the FDA.⁴⁰⁹

The practice of "male-only" drug trials may also result in liability for failure to warn, especially when there is evidence of risk to women.⁴¹⁰ Under a negligence theory of product liability, manufacturers have a duty to warn about not only known risks of a drug, but also foreseeable risks that should have been known.⁴¹¹ If there had been evidence that the drug might be unsafe for use in women (based on animal reproduction studies or physiological gender differences) or if the manufacturer chose not to perform studies that would ascertain the dangers that it should have known, the manufacturer's failure to ascertain and warn against these risks would support a product liability claim, despite compliance with FDA standards.⁴¹²

For health care providers, liability resulting from exclusion

Taylor v. Wyeth Lab., Inc., 362 N.W.2d 293 (Mich. Ct. App. 1984); Barson v. E.R. Squibb & Sons, Inc., 682 P.2d 832 (Utah 1984). These cases are discussed in 1 WOMEN AND HEALTH RESEARCH, *supra* note 3, at 166.

408. See 1 WOMEN AND HEALTH RESEARCH, *supra* note 3, at 166.

409. See *id.* at 165-66 (citing Ellen Flannery & Sanford N. Greenberg, *Liability Exposure for Inclusion of Women as Subjects in Clinical Studies*, in 2 WOMEN AND HEALTH RESEARCH, *supra* note 3, at 91) ("Manufacturers' liability results when, after a drug is on the market, evidence emerges that the drug is more dangerous or less effective in women."); see also Barson v. E.R. Squibb & Sons, Inc., 682 P.2d 832, 836 (Utah 1984) (noting that FDA standards and guidelines for testing are minimum standards).

410. See 1 WOMEN AND HEALTH RESEARCH, *supra* note 3, at 167.

411. See *id.* at 165.

412. If the manufacturer deliberately failed to learn about such risks, it could also be liable for punitive damages. See *id.*

of women from drug trials and other clinical research may arise in the form of medical malpractice claims. Such cases may be based on the negligent prescription of drugs that were not tested on women⁴¹³ or the inappropriate medical treatment of women's health conditions where there is no research data to support efficacy or safety in women.⁴¹⁴ For example, at one time, women had a ten-fold higher risk of dying in the hospital after undergoing coronary angioplasty, a procedure in which a tiny balloon catheter is threaded into a blocked artery and then inflated, thus flattening the blockage.⁴¹⁵ The mortality difference eventually was attributed to the smaller artery size of women, a factor that was not considered when angioplasty was developed.⁴¹⁶ Now that the machines have been scaled down and the inflatable balloons used in women are smaller and more appropriate for their artery size, it would be negligent for a physician to fail to adapt angioplasty procedures to gender differences.

The promulgation of federal regulations and guidelines that promote the inclusion of women in clinical research may both raise the expectations of women for better health care and provide evidence of a standard of health care that recognizes that gender matters. As the standard of care develops to adapt drugs and treatment to gender differences based on clinical research, a physician's failure to adjust his or her clinical practice accordingly might be the basis for a malpractice action.

V. POLICY CONSIDERATIONS

In September, 1992, the Office of Research on Women's Health (ORWH) of the National Institutes of Health, commissioned the Institute of Medicine to establish a Committee on the Ethical and Legal Issues Relating to the Inclusion of Women in

413. See *id.*

414. See *id.* at 166-67. Medical malpractice may also result from misdiagnosis of conditions whose manifestations in women have not been adequately studied or, as a result of gender bias and communication barriers, have not been seriously considered. One clear example of this is ignoring heart attacks in women. When a 42 year old smoker went to a local clinic complaining of chest pains that she had experienced on and off for a year, she was told she probably had gallstones. See LAURENCE & WEINHOUSE, *supra* note 10, at 85. When the pain got worse, she returned to the clinic where, despite the fact that her father and two uncles had died of heart attacks when young, the original diagnosis was affirmed. See *id.* She went home, collapsed from chest pain, and nearly died from a massive heart attack. See *id.* When she was appropriately diagnosed at a larger teaching hospital, cardiologists wondered why no one in the local clinic recognized heart disease in a heavy smoker with chest pain and a family history of death from heart attack. See *id.*

415. See 1 WOMEN AND HEALTH RESEARCH, *supra* note 3, at 104, 105.

416. See *id.* at 105.

Clinical Studies.⁴¹⁷ The Committee was charged with examining the ethical and legal implications of policies that would broaden inclusion of women in clinical trials, including pregnant women and women of childbearing potential.⁴¹⁸ The Committee's recommendations were finalized after passage of the NIH Revitalization Act but prior to publication of the 1994 NIH Guidelines. Much of the Committee's recommendations are still being integrated to varying degrees in NIH policy. Thus, it is important to highlight the most significant social, legal, and ethical considerations that formed the basis for the Committee's recommendations and that are critical to our moving forward in this area. These considerations will be integrated into a discussion of broader policy issues and strategies that address gender bias in all aspects of health care.

A. Justice

The ethical principle of justice is not achieved when the national research agenda does not address women's health issues and when women are subject to treatments that have not been adequately tested on their gender. Toward this goal, the Women's Health Initiative (WHI), the largest U.S. preventive study of its kind, has been established to examine the major causes of and treatments for cardiovascular disease, cancer, and osteoporosis in postmenopausal women.⁴¹⁹ Although it demonstrates NIH's commitment to expanding our knowledge of important women's health issues, the WHI is but one step in achieving justice in our national research agenda.

Where there has not been a fair allocation of research, attention, or resources, "justice may require a policy of preferential treatment . . . in order to remedy a past injustice."⁴²⁰ Our

417. See *id.* at vi.

418. See *id.* The recommendations of the Committee are set out in WOMEN IN HEALTH RESEARCH, *supra* note 3. It is from participation as a member of this Committee that the author endorses the policy recommendations on clinical research. For a listing of the other members of the Committee, see *id.* at iii, iv.

419. See generally NATIONAL INSTITUTES OF HEALTH, OVERVIEW STATEMENT ON WOMEN'S HEALTH INITIATIVE (1995). The WHI has three major components: "a randomized controlled clinical trial of promising but unproven approaches to prevention; an observational study to identify predictors of disease; and a study of community approaches to developing healthful behaviors." *Id.* at 1. The trial will enroll approximately 64,500 postmenopausal women 50-79 years of age and will require a 15 year time frame and an investment of \$628 million. See *id.* at 1-2.

420. See 1 WOMEN AND HEALTH RESEARCH, *supra* note 3, at 5. Furthermore, "[w]omen and men should be enrolled as participants in clinical studies in a manner that ensures that research yields scientifically generalizable results applicable to both genders." *Id.*

enthusiasm for including women and minorities in clinical studies should not mean, however, that these groups now get targeted for coercive activity. Because of the requirements of the NIH Revitalization Act, researchers may feel pressured to recruit and retain participants aggressively from the same groups that historically had been subject to abuse and exploitation.⁴²¹ Voluntariness and informed consent must protect subjects from unethical and coercive treatment.⁴²² Thus, the Committee recommended that, in designing recruitment and consent procedures, principal investigators must be sensitive to the concerns and needs of those groups that have had a history of exploitation or abuse in prior human experimentation.⁴²³

B. Consistency in Federal Regulations: Presumption of Inclusion

Although recent changes in relevant federal policies appear to promote inclusion rather than exclusion, there still remains confusion about the extent to which women of childbearing potential, and particularly pregnant women, are to be included or excluded in clinical research. The NIH and FDA differ in their goals and definitions of clinical trials and research; thus it is important that, wherever possible, federal agencies establish consistent policies in order to avoid regulatory paralysis.⁴²⁴

More specifically, based on an analysis of ethical principles, current statutory and constitutional principles, and the current state of liability concerns, federal policy should assure that both women and men of reproductive age are not excluded by investigators and IRBs from participating in clinical studies.⁴²⁵ "[T]he potential or prospect of becoming pregnant during [a] study may not be used as a justification for precluding or limiting participation" of women of reproductive age.⁴²⁶ This recommendation is based on the principle of respect for persons, as well as a recognition that both men and women must evaluate risks to their reproductive system in the same manner as risks to other organ systems.⁴²⁷ Through the use of the informed consent process, both men and women can evaluate the risks to reproduction and potential offspring.⁴²⁸

421. See *id.* at 9-10.

422. See *id.* at 10.

423. See *id.*

424. See *id.* at 11.

425. See *id.* at 12.

426. *Id.* at 15.

427. See *id.*

428. See *id.* The Committee further recommended that "the participant be permitted to select voluntarily the contraceptive method of his or her choice where

C. Special Considerations for Pregnant Women

Because of significant gaps in knowledge with respect to the treatment of pregnant women, NIH must strongly encourage and facilitate clinical research to advance the treatment of pre-existing medical conditions in women who become pregnant, medical conditions of pregnancy, and conditions that threaten successful course of pregnancy.⁴²⁹ Consequently, pregnant women should be presumed eligible for participation in clinical studies.⁴³⁰ Thus, the Committee advocates that "[e]ven when evidence concerning risks is unknown or ambiguous, the decision about acceptability of risk to the pregnancy or to offspring should be made by the woman as part of the informed consent process."⁴³¹

It is important to note that presuming pregnant women are eligible is not the equivalent of advocating their active recruitment for each clinical study. There may be valid scientific and medical reasons for excluding pregnant women from a certain clinical study.⁴³² After much debate and discussion, most Committee members ultimately endorsed the following recommendations:

Investigators and IRBs may exclude pregnant women from participation only when the IRB finds, and records its finding in writing, that the following standard has been met: (1) there is no prospect of medical benefit to the pregnant woman, and (2) a risk of significant harm to potential offspring is known or can be plausibly inferred.⁴³³

Under this standard, it is expected that an IRB might "exclude pregnant women from the earliest phases of some drug trials, but [that] most clinical studies would remain open to pregnant women."⁴³⁴

there are no relevant study-dependent scientific reasons for excluding certain contraceptives [P]regnancy termination options [should also] be discussed as part of the consent process in clinical studies that pose unknown or foreseeable risks to potential offspring." *Id.*

429. *See id.* at 16.

430. *See id.* at 17. Furthermore, women who are lactating should not be excluded from clinical studies, but the informed consent process should incorporate discussion of any special risks to children. *See id.* at 15.

431. *Id.* at 17.

432. *See id.* The Committee cites the example of a pregnant woman being excluded from a contraception study on a hormone replacement study. *See id.*

433. *Id.* at 18. A finding that trial participation may risk significant harm may be based on evidence from animal studies, in vitro studies, structure-activity relationship data, or previous clinical experience. *Id.*

434. *Id.* It is worth noting that a few of my colleagues on the Committee believed that we should accommodate the conscience of individual investigators who believe that

The principles of respect for persons, justice, and the need for scientific knowledge support the presumption of inclusion, yet existing DHHS regulations relating to pregnant women codify the presumption of exclusion: "no pregnant woman may be a research subject' except under certain conditions."⁴³⁵ When the regulations classify pregnant women as "vulnerable to coercion or undo influence,"⁴³⁶ it suggests that they are less autonomous or more easily exploited by virtue of their pregnancy.⁴³⁷ Subpart B of the DHHS regulations for the protection of human subjects should be repealed or significantly revised to reflect the presumption that pregnant women are as competent as nonpregnant persons to weigh the risks and benefits of participation in an approved clinical study.⁴³⁸ To assure the adequacy of information about the risks and benefits to a woman's pregnancy and potential offspring, strengthened informed consent procedures might include special disclosure statements.⁴³⁹

Furthermore, in recognition of a woman's autonomous decisionmaking and concern for constitutional and ethical principles, the provisions of Subpart B that permit a paternal veto to a pregnant woman's participation in clinical research should be also eliminated.⁴⁴⁰ In the best of all worlds, a pregnant woman should be encouraged to discuss her participation in a clinical trial with the potential offspring's father.⁴⁴¹ Yet

pregnant women should be excluded from a clinical trial. *See id.* However, such a "conscience clause" could be abused significantly and serve indirectly to exclude all pregnant women. *See id.* Such potential abuse, for example, has been experienced in the context of most health care providers refusing to do abortions. *See, e.g.,* Amy Goldstein, *U.S. Abortion Services Drop*, WASH. POST, Jan. 22, 1995, at A1 (reporting that more than 500 U.S. hospitals and clinics have stopped providing abortions since the 1980s).

435. *Id.* at 16 (referring to 45 C.F.R. § 46.207(a)).

436. 45 C.F.R. § 46.111(b).

437. *See id.* Although pregnant women, and more specifically their fetuses, may be considered "vulnerable" in the sense of being susceptible to serious injury, the regulation focuses upon vulnerability in the context of limited decisionmaking capacity. By grouping pregnant women with children, prisoners, mentally disabled persons, and other disadvantaged persons in need of additional protection, it suggests a state of diminished capacity or distrust of their judgment during pregnancy that is misleading and inappropriate.

438. Moreover, the reference to pregnant women as a "vulnerable population[]" in Subpart A, codified at 45 C.F.R. § 46.111(a)(3), should also be eliminated.

439. The Committee suggested that the disclosure statement might include: "If you are pregnant or contemplating pregnancy, we urge you to consult your obstetrical care provider before deciding about participation in this study. Participation in this study may (does) pose a risk of (significant) harm to your pregnancy and/or your potential baby." 1 WOMEN AND HEALTH RESEARCH, *supra* note 3, at 196 (emphasis removed).

440. *See id.* at 197. Refer to subpart III(B)(1) *supra*.

441. *See* 1 WOMEN AND HEALTH RESEARCH, *supra* note 3, at 197 (recognizing that the father may have a strong emotional attachment to his unborn child).

women, not investigators or the state, are in the best position to determine whether to consult with the future father. To have the power to veto the participation in research gives men unreasonable control over a woman's bodily integrity and medical decisionmaking authority.⁴⁴² In fact, it is inconsistent that once a child is born, federal regulations require, under certain circumstances, only one parent's permission to enroll a child in clinical research.⁴⁴³

Until Subpart B is amended, we will continue to face mixed messages from the regulatory arena. Special rules for pregnant women as vulnerable often get carried over into special rules for all women of childbearing potential. Ironically, this would undermine our very attempts to expand the numbers of women in clinical studies. More importantly, we must also recognize that such an inference that pregnant women are less autonomous will perpetuate gender bias in other areas of health care. To date, the new NIH Guidelines are silent with respect to special rules for pregnant women. To further complicate the regulatory landscape, the FDA has yet to establish guidelines on including pregnant women in drug trials.⁴⁴⁴

D. Addressing Gender Bias

Gender bias in clinical research must be placed in its social and ethical context. Two forms of gender bias may impact on the design and conduct of clinical studies: male bias (adopting a male perspective) and the male norm (the tendency to use males as the standard and females as problematic).⁴⁴⁵ These biases, in turn, are further perpetuated in the delivery of women's health care.

Unconscious biases may permeate the entire scientific research process, influencing the research topics selected, the concepts examined, the study design, and the research participants chosen for inclusion.⁴⁴⁶ Clearly, one way to address such gender biases may be to increase the numbers of women scientists active in clinical research. Toward this goal, one of the

442. *See id.*

443. *See id.*

444. The CDC Policy, refer to note 233 *supra*, however, does provide that "[i]nformation on adverse differences in outcome or risk profiles for pregnant women may be reason for exclusion." 60 Fed. Reg. 47,949. It further states that "pregnancy status may need to be determined prior to enrollment for some studies and, if necessary, during an intervention to safeguard the participants' health." *Id.*

445. *See* 1 WOMEN AND HEALTH RESEARCH, *supra* note 3, at 8.

446. *See id.*

major priorities of the Office of Research on Women's Health (ORWH) is to foster the recruitment and promotion of women in biomedical careers.⁴⁴⁷

In addition to increasing the number of women in biomedical careers, the ORWH, in collaboration with other governmental agencies and women's health and professional organizations, is examining "the appropriate integration" of women's health issues into medical school curricula.⁴⁴⁸ Health care professionals not only need to understand basic female physiology and reproductive biology, but also must understand aspects of disease that differ in women. Just as significantly, the goal of medical education should be to create "an understanding of how medicine has historically perpetuated sex-role stereotypes in definitions of health, illness and normality, through research and clinical practice."⁴⁴⁹ Thus, if physicians are going to be competent to comprehensively address women's health needs, they must be able to adopt attitudes and behaviors that are culturally⁴⁵⁰ and gender sensitive, including an appreciation of gender differences in communication, interaction, and clinical decisionmaking.⁴⁵¹

VI. CONCLUSION

In the end, society must trust women to make decisions about their own health and a healthy future with their families. Gender bias in clinical research has left us with a large amount of incomplete or meaningless information on how best to address women's health needs. It has left pregnant women and their physicians totally in the dark. The common label that appears on

447. See generally OFFICE OF RESEARCH ON WOMEN'S HEALTH, NATIONAL INSTITUTES OF HEALTH, *WOMEN IN BIOMEDICAL CAREERS* (1992). Issues covered include: recruiting women in biomedical careers, role of models and mentors, career paths and rewards, reentry into a biomedical career, family responsibilities, research initiatives on women's health, gender sensitivity, and minority women and science. See *id.* at 8-13.

448. See HOUSE COMM. ON APPROPRIATIONS, H.R. REP. NO. 156, 103d Cong., 1st Sess. 81 (1993); see also SENATE APPROPRIATIONS COMM., S. REP. NO. 397, 102d Cong., 2d Sess. 143 (1992). S. 1569 would have established an Office of Women's Health to work with other governmental health agencies to advance research on women's health, facilitate the employment of women as scientists, and expand medical school curriculum on women's health. See S. REP. NO. 397, *supra*, at 49-50.

449. Susan Phillips, *The Social Context of Women's Health: Goals and Objectives for Medical Education*, 152 CAN. MED. ASS'N J. 507, 509 (1995).

450. Health care providers must be particularly attentive to how women's health needs reflect differences in race, class, ethnicity, culture, sexual orientation, and socio-economic status. See *id.* at 510.

451. See COUNCIL ON GRADUATE MEDICAL EDUC., FIFTH REPORT: WOMEN AND MEDICINE 23 (1995) (advocating a "new paradigm" to improve health care, including attention to prevention, community approaches, and education).

all drugs is symbolic: “It is also not known whether [this drug] can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. [This drug] should be given to a pregnant woman only if clearly needed.”⁴⁵² It is more than a warning for pregnant women and their physicians; rather it is a warning to all of us that if we do not presume that all women can be trusted to make decisions about clinical research and health care, we will never eradicate gender bias.

452. 21 C.F.R. § 201.57(f)(6)(i)(c).